



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/US97/21434 <b>(22) International Filing Date:</b> 25 November 1997 (25.11.97) <b>(30) Priority Data:</b> 60/032,509                      3 December 1996 (03.12.96)                      US <b>(71) Applicant (for all designated States except US):</b> ELI LILLY AND COMPANY [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> GOODSON, Theodore, Jr. [US/US]; 4045 Devon Drive, Indianapolis, IN 46226 (US). HARPER, Richard, W. [US/US]; 6401 Spring Mill Road, Indianapolis, IN 46260 (US). HERRON, David, K. [US/US]; 5945 Andover Road, Indianapolis, IN 46220 (US). <b>(74) Agents:</b> PALMBERG, Arleen_ et al.; Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285 (US).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> PHENYL GLYOXAMIDES AS sPLA <sub>2</sub> INHIBITORS  <b>(57) Abstract</b>  A class of novel phenyl glyoxamides is disclosed together with the use of such compounds for inhibiting sPLA <sub>2</sub> mediated release of fatty acids for treatment of conditions such as septic shock.		

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PHENYL GLYOXAMIDES AS SPLA<sub>2</sub> INHIBITORS

5 This invention relates to novel substituted phenyl glyoxamides useful for inhibiting sPLA<sub>2</sub> mediated release of fatty acids for conditions such as septic shock.

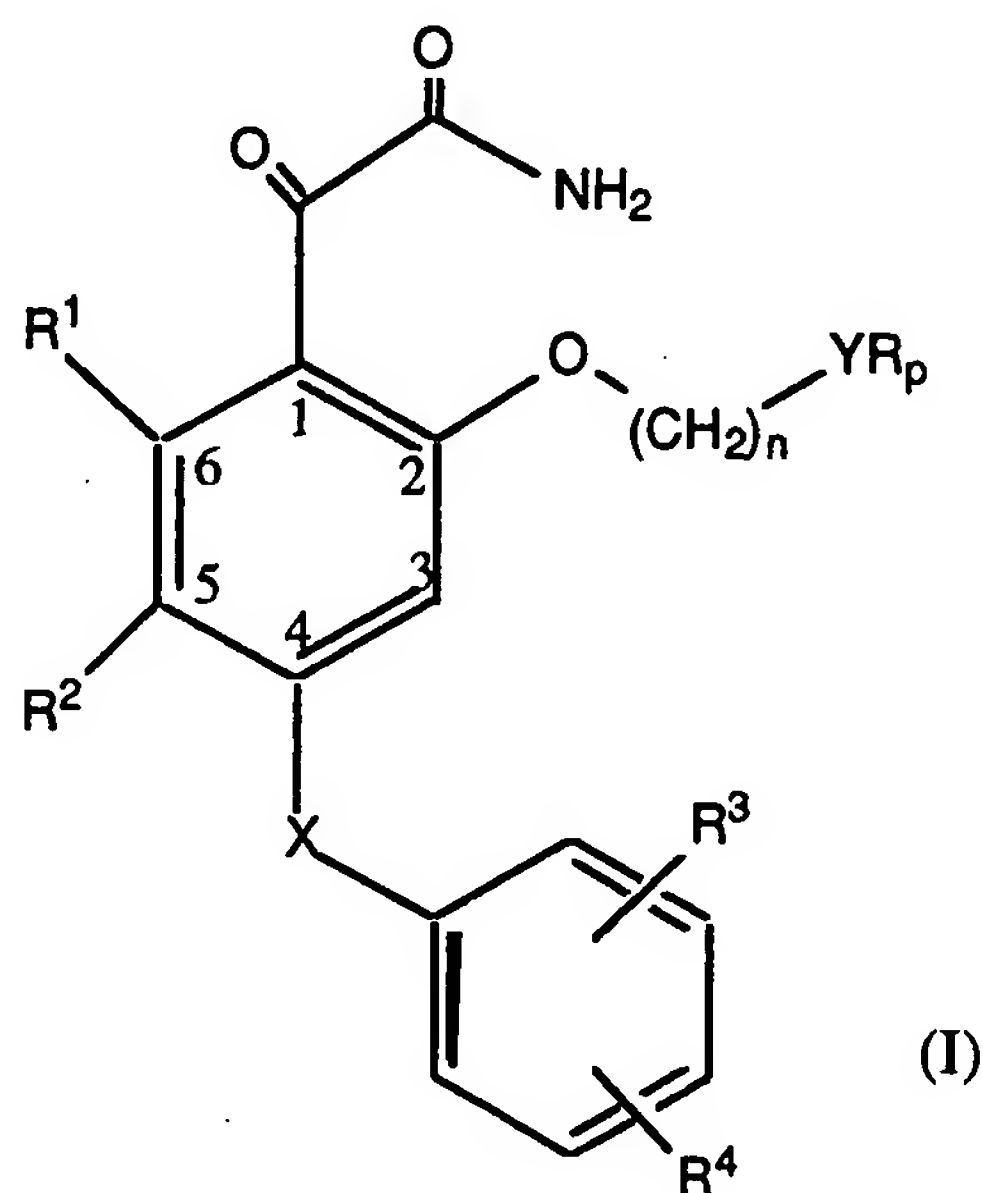
10 The structure and physical properties of human non-pancreatic secretory phospholipase A<sub>2</sub> (hereinafter called, "sPLA<sub>2</sub>") has been thoroughly described in two articles, namely, "Cloning and Recombinant Expression of Phospholipase A<sub>2</sub> Present in Rheumatoid Arthritic Synovial  
15 Fluid" by Seilhamer, Jeffrey J.; Pruzanski, Waldemar; Vadas Peter; Plant, Shelley; Miller, Judy A.; Kloss, Jean; and Johnson, Lorin K.; The Journal of Biological Chemistry, Vol. 264, No. 10, Issue of April 5, pp. 5335-5338, 1989; and "Structure and Properties of a Human Non-  
20 pancreatic Phospholipase A<sub>2</sub>" by Kramer, Ruth M.; Hession, Catherine; Johansen, Berit; Hayes, Gretchen; McGray, Paula; Chow, E. Pingchang; Tizard, Richard; and Pepinsky, R. Blake; The Journal of Biological Chemistry, Vol. 264, No. 10, Issue of April 5, pp. 5768-5775, 1989; the  
25 disclosures of which are incorporated herein by reference.

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It is believed that sPLA<sub>2</sub> is a rate limiting enzyme in the arachidonic acid cascade which hydrolyzes membrane phospholipids. Thus, it is important to develop compounds which inhibit sPLA<sub>2</sub> mediated release of fatty acids (e.g., arachidonic acid). Such compounds would be of value in general treatment of conditions induced and/or maintained by overproduction of sPLA<sub>2</sub>; such as septic shock, adult respiratory distress syndrome, pancreatitis, trauma-induced shock, bronchial asthma, allergic rhinitis, rheumatoid arthritis etc.

It is desirable to develop new compounds and treatments for sPLA<sub>2</sub> induced diseases.

This invention provides compounds of the formula I



wherein:

- X is -O- or -(CH<sub>2</sub>)<sub>m</sub>-, where m is 0 or 1;
- Y is -CO<sub>2</sub>-, -PO<sub>3</sub>-, -SO<sub>3</sub>-;
- R is independently -H or -(C<sub>1</sub>-C<sub>4</sub>)alkyl;
- R<sup>1</sup> and R<sup>2</sup> are each independently -H, halo or -(C<sub>1</sub>-C<sub>4</sub>)alkyl;

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$R^3$  and  $R^4$  are each independently -H, -(C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, (C<sub>1</sub>-C<sub>4</sub>)alkylthio, halo, phenyl or phenyl substituted with halo;

$n$  is 1-8; and

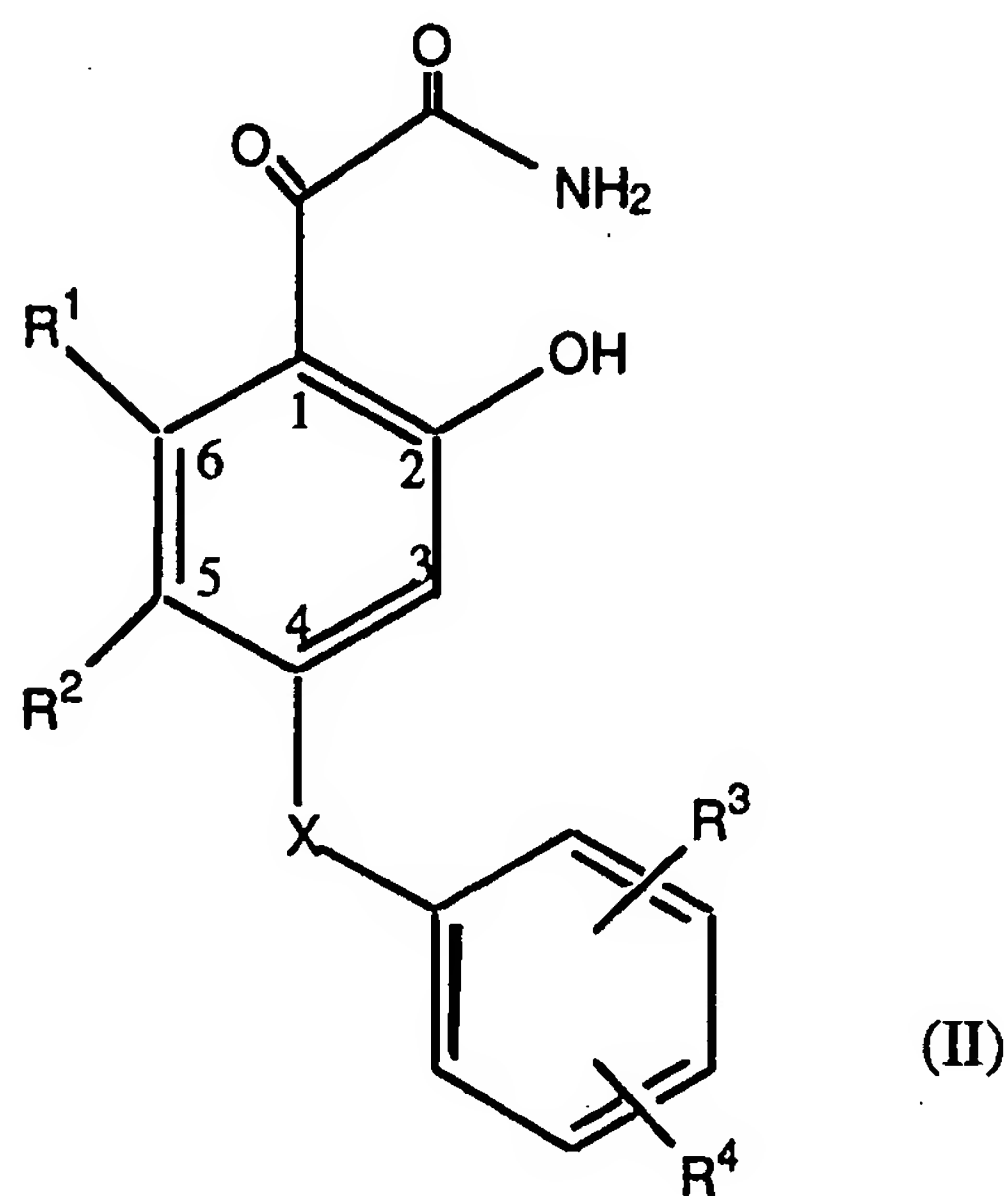
5  $p$  is 1 when  $Y$  is -CO<sub>2</sub>- or -SO<sub>3</sub>- and 1 or 2 when  $Y$  is -PO<sub>3</sub>-;

or a pharmaceutically acceptable salt thereof.

These phenyl glyoxamides are effective in inhibiting human sPLA<sub>2</sub> mediated release of fatty acids.

10

The present also provides new intermediate compounds of formula II



15

wherein:

$X$  is -O- or -(CH<sub>2</sub>) <sub>$m$</sub> -, where  $m$  is 0 or 1;

20  $R^1$  and  $R^2$  are each independently -H, halo or -(C<sub>1</sub>-C<sub>4</sub>)alkyl and

$R^3$  and  $R^4$  are each independently -H, -(C<sub>1</sub>-C<sub>4</sub>)alkyl, -(C<sub>1</sub>-C<sub>4</sub>)alkoxy, (C<sub>1</sub>-C<sub>4</sub>)alkylthio, halo, phenyl or phenyl substituted with halo.

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The compounds of formula II are useful as intermediates in preparing the compounds of formula I.

5 This invention is also a pharmaceutical formulation comprising a compound of formula I in association with one or more pharmaceutically acceptable diluents, carriers and excipients.

10 This invention is also a method of inhibiting sPLA<sub>2</sub> comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of formula I.

15 According to a further aspect of the present invention, there is provided a method of selectively inhibiting sPLA<sub>2</sub> in a mammal in need of such treatment comprising administering to said mammal a therapeutically effective amount of a compound of formula I.

20 This invention also provides a method of alleviating the pathological effects of septic shock, adult respiratory distress syndrome, pancreatitis, trauma-induced shock, bronchial asthma, allergic rhinitis, rheumatoid arthritis, and related diseases which comprises administering to a mammal in need of such treatment a therapeutically effective amount of the compound of formula I in an amount sufficient to inhibit sPLA<sub>2</sub> mediated release of fatty acid and to thereby  
25 inhibit or prevent the arachidonic acid cascade and its deleterious products.

30 Other objects, features and advantages of the present invention will become apparent from the subsequent description and the appended claims.

#### Detailed Description of the Invention

##### Definitions:

35 As used herein, the term, "alkyl" by itself or as part of another substituent means, unless otherwise defined, a straight or branched chain monovalent

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hydrocarbon radical such as methyl, ethyl, n-propyl, isopropyl, n-butyl, tertiary butyl and isobutyl.

The term "halo" means chloro, fluoro, bromo or iodo.

5           The term "(C<sub>1</sub>-C<sub>4</sub>) alkoxy" denotes defines a straight or branched alkyl chain having one to four carbon atoms attached to the remainder of the molecule by an oxygen atom. Typical (C<sub>1</sub>-C<sub>4</sub>) alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, t-  
10 butoxy and like.

          The term "(C<sub>1</sub>-C<sub>4</sub>)alkylthio" defines a straight or branched alkyl chain having one to four carbon atoms attached to the remainder of the molecule by a sulfur atom. Typical (C<sub>1</sub>-C<sub>4</sub>)alkylthio groups include  
15 methylthio, ethylthio, propylthio, butylthio and the like.

          The salts of the above phenyl glyoxamides are an additional aspect of the invention. In those instances where the compounds of the invention possess  
20 acidic functional groups various salts may be formed which are more water soluble and physiologically suitable than the parent compound. Representative pharmaceutically acceptable salts include but are not limited to the alkali and alkaline earth salts such as  
25 lithium, sodium, potassium, calcium, magnesium, aluminum and the like. Salts are conveniently prepared from the free acid by treating the acid in solution with a base or by exposing the acid to an ion exchange resin.

          Examples of pharmaceutically acceptable organic  
30 bases which may be used to prepare pharmaceutically acceptable salts include ammonia, amines such as triethanolamine, triethylamine, ethylamine, and the like.

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Preferred Compounds of the Invention

Preferred substituent groups of compounds of formula (I) include the following:

5

- (a) X is O;
- (b) X is CH<sub>2</sub>;
- (c) Y is -CO<sub>2</sub>- or -PO<sub>3</sub>- ;
- (d) R, R<sup>1</sup> and R<sup>2</sup> are -H;
- 10 (e) R<sup>3</sup> and R<sup>4</sup> are each independently -H, -  
m-(C<sub>1</sub>-C<sub>4</sub>)alkyl, -m-(C<sub>1</sub>-C<sub>4</sub>)alkoxy, -m-halo, -  
m-(C<sub>1</sub>-C<sub>4</sub>)alkylthio, or m-phenyl substituted with halo;
- (f) R<sup>3</sup> is independently -H, -o-(C<sub>1</sub>-C<sub>4</sub>)alkyl, -  
o-(C<sub>1</sub>-C<sub>4</sub>)alkoxy, o-halo, -o-(C<sub>1</sub>-C<sub>4</sub>)alkylthio, o-phenyl or  
15 o-phenyl substituted with halo;
- (g) R<sup>3</sup> and R<sup>4</sup> are each independently -H or m-phenyl  
or -m-3-fluorophenyl;
- (h) R<sup>3</sup> and R<sup>4</sup> are each independently -H, o-phenyl  
or -o-3-fluorophenyl; and
- 20 (i) n is 4-5.

Preferred substituent groups of compounds of formula (II) include the following:

- (aa) R<sup>1</sup> and R<sup>2</sup> are -H;
- 25 (bb) R<sup>3</sup> and R<sup>4</sup> are each independently -H, -  
m-(C<sub>1</sub>-C<sub>4</sub>)alkyl, -m-(C<sub>1</sub>-C<sub>4</sub>)alkoxy, -m-halo, -  
m-(C<sub>1</sub>-C<sub>4</sub>)alkylthio, or m-phenyl substituted with halo;
- (cc) R<sup>3</sup> is independently -H, -o-(C<sub>1</sub>-C<sub>4</sub>)alkyl, -  
o-(C<sub>1</sub>-C<sub>4</sub>)alkoxy, o-halo, -o-(C<sub>1</sub>-C<sub>4</sub>)alkylthio, o-phenyl or  
30 o-phenyl substituted with halo;
- (dd) R<sup>3</sup> and R<sup>4</sup> are each independently -H or m-phenyl  
or -m-3-fluorophenyl; and
- (ee) R<sup>3</sup> and R<sup>4</sup> are each independently -H, o-phenyl  
or -o-3-fluorophenyl.

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Further typical examples of compounds of formula I which are useful in the present invention include:

2-(6-carboxyhex-1-yloxy)-4-(3-phenylphenoxy)-5-ethylphenylglyoxamide;

Sodium 2-(8-carboxyoct-1-yloxy)-4-benzyl-5-t-butyl-6-propylphenylglyoxamide;

2-(4-carboxybut-1-yloxy)-4-(2-methoxybenzyl)-6-chlorophenylglyoxamide;

2-hydroxy-4-(2-methoxybenzyl)-6-chlorophenylglyoxamide;

2-(3-carboxyprop-1-yloxy)-4-(2-ethylthio-6-fluorobenzyl)phenylglyoxamide;

Potassium 2-(4-carboxybut-1-yloxy)-4-(3,5-diphenyl)benzyl)-6-phenylglyoxamide;

2-(3-carboxyprop-1-yloxy)-4-(3-fluoro-5-phenyl)phenyl-5-propylphenylglyoxamide;

2-hydroxy-4-(3-fluoro-5-phenyl)phenyl-5-propylphenylglyoxamide;

2-(2-carboxyethoxy)-4-thiophenyl-5-fluorophenylglyoxamide;

Calcium 2-(4-carboxybut-1-yloxy)-4-(2,6-dimethyl)phenyl-phenylglyoxamide;

2-(3-carboxyprop-1-yloxy)-4-(3,5-difluorobenzyl)phenylglyoxamide;

2-(2-carboxethoxy)-4-(4-(4-chlorophenyl)benzyl)-5-bromophenylglyoxamide;

Magnesium 2-(3-carboxyprop-1-yloxy)-4-(3-ethylphenyl)-6-methylphenylglyoxamide

2-(4-carboxybut-1-yloxy)-4-(2-ethyl-6-methoxy)benzyl-5,6-dimethylphenylglyoxamide;

2-hydroxy-4-(2-ethyl-6-methoxy)benzyl-5,6-dimethylphenylglyoxamide;

2-(2-carboxyethoxy)-4-(3-methylthio-5-phenyl)benzyl-phenylglyoxamide;

2-(4-carboxybut-1-yloxy)-4-(3-propyl-5-chloro)benzyl-phenylglyoxamide;

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2-(3-carboxyprop-1-yloxy)-4-(5-(3-chlorophenyl)benzyl-phenylglyoxamide;

2-(2-carboxyethoxy)-4-(3-phenyl-5-fluorobenzyl)phenylglyoxamide;

5 2-(3-carboxyprop-1-yloxy)-4-(4-methyl)benzyl-phenylglyoxamide;

2-(4-carboxybut-1-yloxy)-4-(2,4-dimethyl)benzyl-phenylglyoxamide;

2-hydroxy-4-(2,4-dimethyl)benzyl-phenylglyoxamide;

10 2-(carboxymethoxy)-4-(4-propyl)phenyl-5-methylphenylglyoxamide;

Lithium 2-(2-carboxyethoxy)-4-(3-(3-fluorophenyl)benzyl-6-butylphenylglyoxamide;

15 2-(3-carboxyprop-1-yloxy)-4-(3,5-diethoxy)benzyl-5-ethylphenylglyoxamide;

2-((3-dimethoxyphosphonoyl)prop-1-yloxy)-4-phenoxyphenylglyoxamide;

2-(2-phosphonoyl)ethoxy-4-benzyl-5-methyl-6-fluorophenylglyoxamide;

20 Sodium 2-(diethoxyphosphonoyl)methoxy-4-benzylphenylglyoxamide;

2-((3-phosphonoyl)prop-1-yloxy)-4-(2-methyl)benzylphenylglyoxamide;

2-hydroxy-4-(2-methyl)benzylphenylglyoxamide;

25 2-(2-dimethoxyphosphonoyl)ethoxy-4-(3,5-dichlorophenylphenyl)phenylglyoxamide;

2-((4-diethoxyphosphonoyl)but-1-yloxy)-4-(6-phenyl)phenylglyoxamide;

30 2-((3-phosphonoyl)prop-1-yloxy)-4-(2-fluoro-4-phenyl)phenylglyoxamide;

2-(dimethoxyphosphonoyl)methoxy-4-phenyl-5-fluoro-6-methylphenylglyoxamide;

Potassium 2-((4-phosphonoyl)but-1-yloxy)-4-(2,6-dimethoxy)phenyl-5-methylphenylglyoxamide;

35 2-(phosphonoyl)ethoxy-4-(4-propyl)benzyl-5-fluorophenylglyoxamide;

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2-((4-diethoxyphosphonyl)but-1-yloxy)-4-(3-(4-fluorophenyl)benzyl)-6-methylphenylglyoxamide;

2-(dimethoxyphosphonyl)methoxy-4-(2,6-diethylbenzyl)-5-methylphenylglyoxamide;

5 2-(methoxysulfonyl)methoxy-4-(3,5-diethyl)benzylphenylglyoxamide;

2-sulfonylethoxy-4-(3-methylthio-5-phenyl)benzylphenylglyoxamide;

10 2-hydeoxy-4-(3-methylthio-5-phenyl)benzylphenylglyoxamide;

Calcium 2-((4-sulfonyl)but-1-yloxy)-4-(6-chloro)phenoxy-phenylglyoxamide;

2-((3-sulfonyl)prop-1-yloxy)-4-benzylphenylglyoxamide;

15 2-sulfonylethoxy)-4-(4-(4-fluorophenyl))benzylphenylglyoxamide;

2-((3-sulfonyl)prop-1-yloxy)-4-(4-methyl)phenoxy-phenylglyoxamide;

20 2-(methoxysulfonyl)methoxy-4-(2,4-dimethyl)benzylphenylglyoxamide;

2-(4-methoxysulfonyl)but-1-yloxy-4-(4-propyl)benzyl-5-methylphenylglyoxamide;

2-(2-ethoxysulfonyl)ethoxy-4-(3-(3-fluorophenyl)phenoxy-6-butylphenylglyoxamide;

25 2-hydroxy-4-(3-(3-fluorophenyl)phenoxy-6-butylphenylglyoxamide;

Magnesium 2-((3-methoxysulfonyl)prop-1-yloxy)-4-(3,5-diethoxy)benzyl-5-ethylphenylglyoxamide;

30 2-((3-carboxymethoxy)prop-1-yloxy)-4-phenoxyphenylglyoxamide;

2-(2-ethoxycarbonyl)ethoxy-4-benzyl-5-methyl-6-fluorophenylglyoxamide;

2-(propoxycarbonyl)methoxy-4-benzylphenylglyoxamide;

35 2-((3-methoxycarbonyl)prop-1-yloxy)-4-(4-phenyl)phenoxy-phenylglyoxamide;

2-(ethoxycarbonyl)ethoxy-4-(2,6-difluorophenylphenyl)phenylglyoxamide;

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2-((4-methoxycarbonyl)but-1-yloxy)-4-(3-phenyl)phenoxy-5-methylphenylglyoxamide;

2-(3-propoxycarbonyl)prop-1-yloxy-4-phenyl-6-ethylphenylglyoxamide;

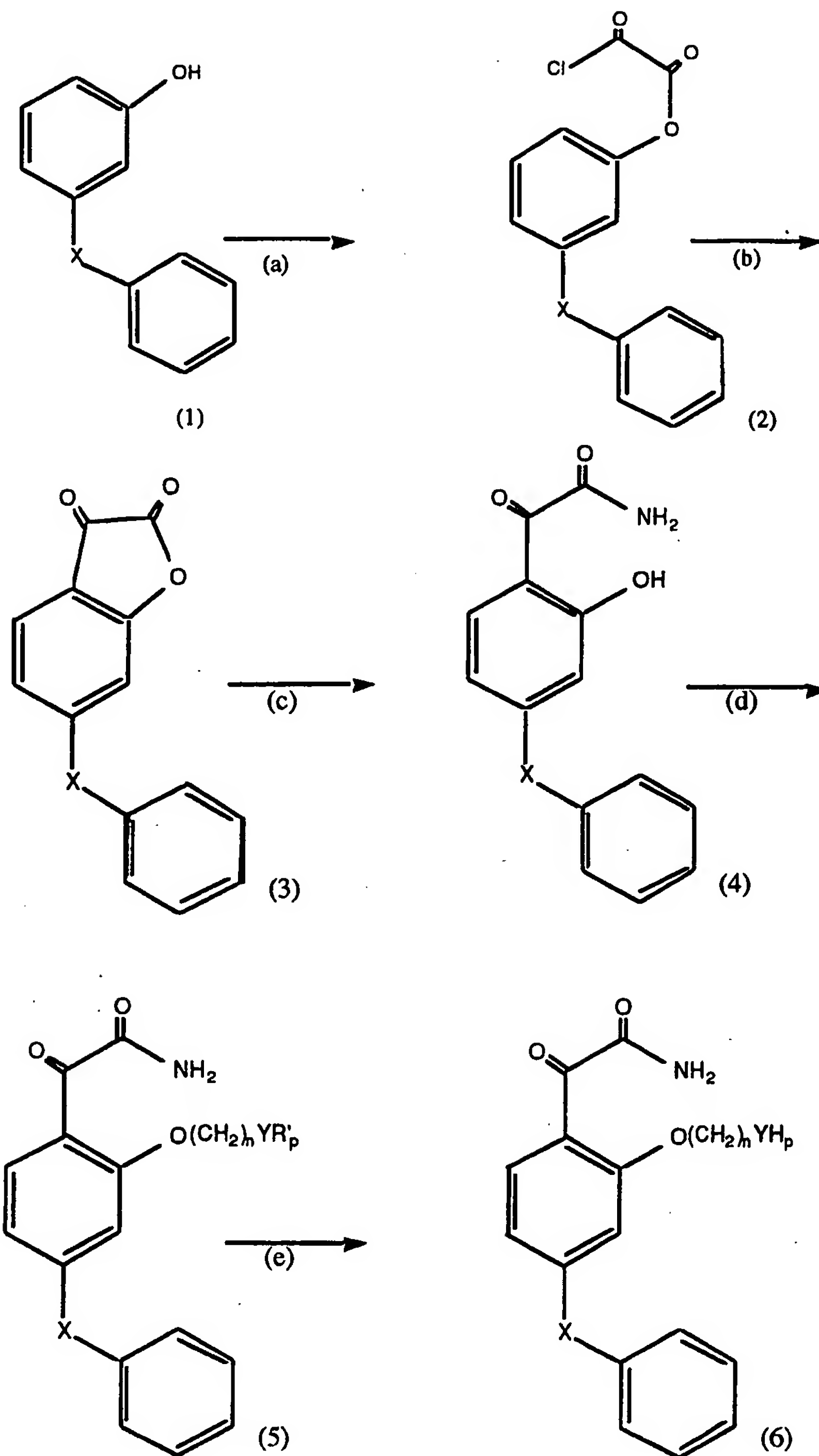
5 2-(methoxycarbonyl)methoxy-4-phenoxy-5-fluoro-6-methylphenylglyoxamide.

#### Synthesis Methods

10 Compounds where  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  are H, and X, Y and n and p are as defined above can be prepared according to the following Scheme I.

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Scheme I



R' is  $-(\text{C}_1\text{-C}_4)\text{alkyl}$

Reflux of (1) with oxalyl chloride in an alkyl halide solvent, such as chloroform, using 4-N,N'

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dimethylamino pyridine as a catalyst achieves intermediate (2).

Under Friedel-Crafts conditions, using a suitable Lewis-acid catalyst such as aluminum chloride, compound (2) is internally cyclized to form compound (3). The reaction is preferably conducted at temperatures from about 0°C to room temperature and allowed to proceed for about 24 hours.

Aminolysis of (3) to amide (4) can be achieved by treatment with concentrated ammonium hydroxide.

Alkylation of the hydroxyl of compound (4) can be readily achieved by treatment with an appropriate alkylating agent, such as  $\text{Br}(\text{CH}_2)_n\text{Y}$ , where Y is  $-\text{CO}_2\text{R}$ ,  $-\text{PO}_3\text{R}_2$  or  $\text{SO}_3\text{R}$  and R is  $-(\text{C}_1\text{-C}_4)\text{alkyl}$ , to form intermediate (5). The reaction is preferably conducted in an aprotic polar solvent, such as dimethyl formamide, in the presence of potassium carbonate and a suitable catalyst, such as potassium iodide.

Conversion of (5) to the carboxylic or sulfonic acid or acid salt (6) may be achieved by treatment with an appropriate base, such as aqueous sodium hydroxide, in a polar protic solvent, such as methanol.

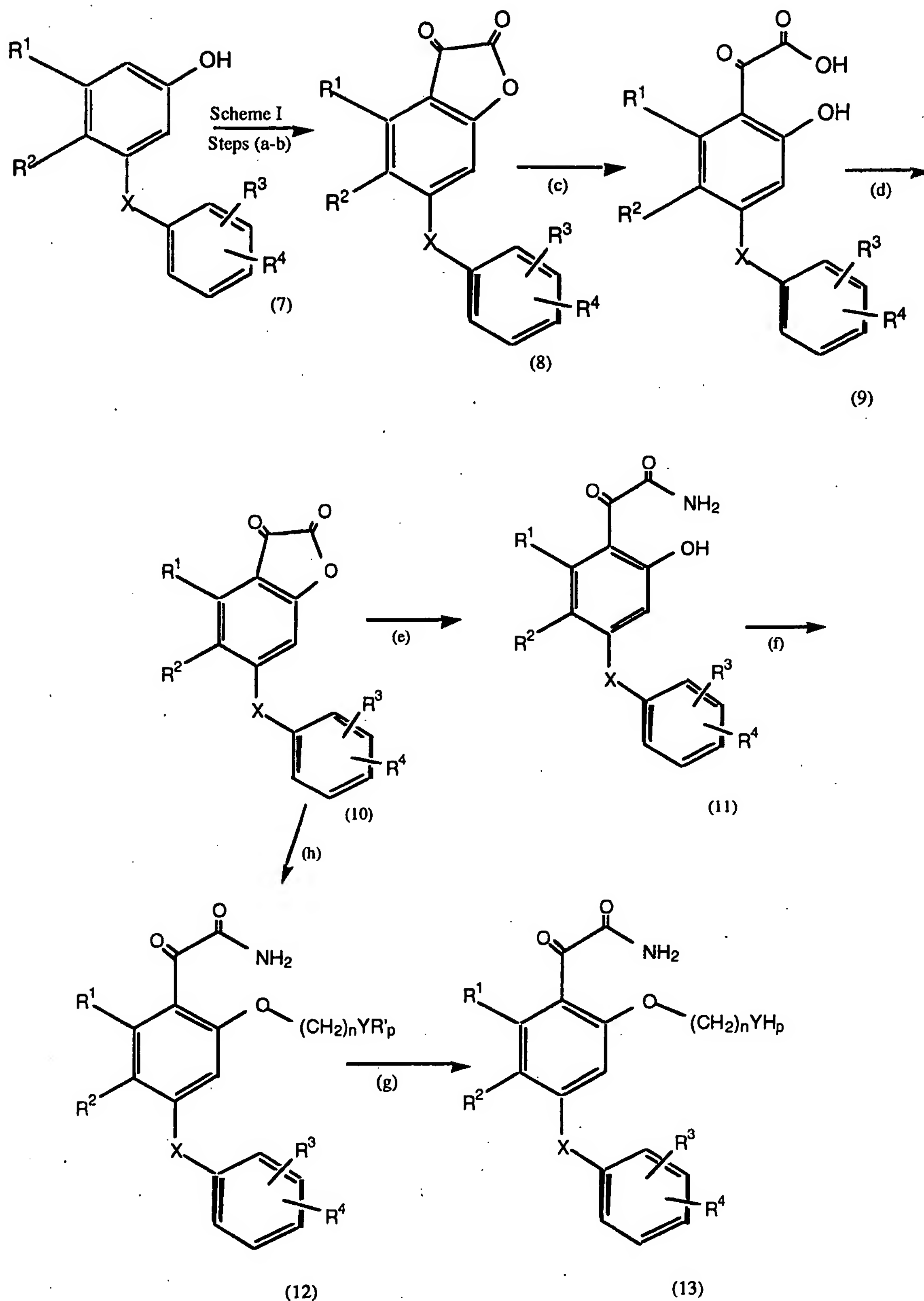
When n is 2, a bromoacetal must be employed as an alkylating agent to achieve the carboxylic acid (6). The alkylated moiety (5) is then converted to the acid (6) by oxidizing with sodium dichromate in aqueous conditions.

When Y is  $-\text{PO}_3-$ , conversion to the acid (6), is preferably conducted in an alkyl halide solvent, such as methylene chloride, using a dealkylating agent, such as trimethylsilyl bromide, and an excess of potassium carbonate, followed by treatment with methanol.

When  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$  or  $\text{R}^4$  are other than hydrogen, the preparation proceeds as described in Scheme II on the following page.

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## Scheme II



5  $R'$  is as defined in Scheme I.

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An appropriately  $R^1$ ,  $R^2$  substituted phenol (7) is converted to lactone (8) following the procedures described in Scheme I, steps (a-b) above.

Conversion to the intermediate (9) is accomplished by reacting (2a) with an aqueous acid, such as hydrochloric acid which affords removal of aluminum chloride from the reaction. Acid (9) is converted to the corresponding acid chloride using oxalyl chloride with dimethyl formamide as a catalyst. The acid chloride is  
10 recycled to the lactone (10) on removal of the solvent, preferably under vacuum. The lactone (10) is converted to the glyoxamide (11) by treatment with an excess of ammonia as described in Scheme I, step (c), above.

Alkylation of (11) to prepare the ester (12),  
15 followed by conversion to the acid is accomplished according to the procedure outlined in Scheme I, steps (d) and (e).

Alternately, conversion of (10) to (12) can be accomplished in a one-pot procedure by treating the  
20 lactone (10) with sodium amide in an aprotic polar solvent, such as dimethylformamide, preferably at temperatures of from about 0°C to 20°C, followed by alkylation with an appropriate alkyl halide.

The intermediates and final products may be  
25 isolated and purified by conventional techniques, for example by concentration of the solvents, followed by washing of the residue with water, then purification by conventional techniques such as chromatography or recrystallization.

30 It will be readily appreciated by the skilled artisan that the starting materials are either commercially available or can be readily prepared by known techniques from commercially available starting materials. For example, when X is oxygen, starting  
35 material (1) can be readily prepared by coupling an appropriately substituted phenol with an appropriately



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substituted phenyl halide to prepare the anisole, under Ullmann-type conditions, by refluxing the phenol and phenyl halide in the presence of an excess of potassium carbonate and cupric oxide in an aprotic polar solvent such as pyridine. The reaction is preferably conducted under a argon blanket and is substantially complete in from 1 to 48 hours.

Demethylation of the anisole is achieved by refluxing for from 1 to 24 hours using an ether cleaving reagent, such as 40% hydrogen bromide in acetic acid, in a polar protic solvent, such as acetic acid to prepare (1).

All other reactants used to prepare the compounds in the instant invention are commercially available.

The following examples further illustrate the preparation of the compounds of this invention. The examples are illustrative only and are not intended to limit the scope of the invention in any way.

The following abbreviations are used in Examples 1 to 13 below.

HOAc is acetic acid  
HBr is hydrogen bromide  
EtOAc is ethyl acetate  
NaHCO<sub>3</sub> is sodium bicarbonate  
Na<sub>2</sub>SO<sub>4</sub> is sodium sulfate  
CHCl<sub>3</sub> is chloroform  
NH<sub>4</sub>OH is ammonium hydroxide  
HCl is hydrochloric acid  
CuO is copper (II) oxide  
MgSO<sub>4</sub> is magnesium sulfate  
DAP is diammonium phosphate  
AlCl<sub>3</sub> is aluminum chloride  
K<sub>2</sub>CO<sub>3</sub> is potassium carbonate  
CH<sub>2</sub>Cl<sub>2</sub> is methylene chloride  
NH<sub>3</sub> is ammonia  
DMF is dimethyl formamide

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KI is potassium iodide

MeOH is methanol

NaH is sodium hydride

NaOH is sodium hydroxide

5 DMAP dimethyl amino (pyridine)

## Example 1

## 2-(5-carboxypent-1-yloxy)-4-phenoxyphenylglyoxamide

10

## A. Preparation of 3-phenoxyanisole

3-Methoxyphenol (287.4 g; 2.3 Mol), 316.0 g (2.0 Mol) of bromobenzene, 552 g (4.0 Mol) of K<sub>2</sub>CO<sub>3</sub>, 12.0 g (0.19 Mol) of activated copper (prepared according to Org. Syn. Coll. Vol. II, p 445-6), Cu(II) acetate hydrate 2.0 g (11 mMol), CuO powder (2.0 g; 25 mMol), and 2.0 g of copper sulfate (13 mMol) were combined in 1500 mL of dry pyridine. The resultant mixture was heated under reflux for 3 days. After cooling, the mixture was concentrated under reduced pressure, then treated with 6N HCl. Extraction was carried out with ether. The combined organics were washed with water, dilute NaOH, and water, then concentrated under reduced pressure. The residue was distilled in vacuo to give 3-phenoxyanisole, distilling at 138-40°C/2 mm pressure, 119 g (75% yield).

25

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 3.81 (s, 3H), 6.61 (m, 2H), 6.68 (d, J=7.8Hz, 1H), 7.06 (d, J=8.3, 2H), 7.14 (t, J=7.4Hz, 1H), 7.25 (t, J=8.4Hz, 1H), 7.37 (t, J=7.8Hz, 2H).

## 30 B. Preparation of 3-phenoxyphenol

3-Phenoxyanisole (8.3 g) was added to a mixture of 50 mL of 40% HBr and 100 mL of glacial acetic acid. The resultant mixture was heated under reflux for 48 hours, then cooled and concentrated under reduced pressure. The residue was taken up in EtOAc, washed with water, saturated NaHCO<sub>3</sub>, and brine. After drying with MgSO<sub>4</sub>,

35

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and concentration under reduced pressure, 3-phenoxyphenol was obtained and used without further purification.

C. Preparation of 3-phenoxyphenylglyoxylic acid lactone

5        3-Phenoxyphenol was combined with oxalyl chloride  
      (6.5 mL; 2 eq) and 0.1 g of DMAP (catalytic), in 30 mL of  
      CHCl<sub>3</sub>. The mixture was heated under reflux for 10 hours,  
      then cooled and concentrated under reduced pressure. The  
      residue was dissolved in 20 mL of dichloroethane and  
10       added dropwise at room temperature to a slurry of AlCl<sub>3</sub>  
      in 100 mL of dichloroethane. The mixture was allowed to  
      stir overnight at room temperature, then poured  
      cautiously into water and allowed to stir for one hour to  
      effect hydrolysis. Extraction was carried out with  
15       methylene chloride. The combined organics were washed  
      with brine and dried over MgSO<sub>4</sub>. After concentration  
      under reduced pressure, the product was obtained as a  
      yellow solid (4.1 g). A sample was recrystallized from  
      CH<sub>2</sub>Cl<sub>2</sub>/ether for characterization.  
20       mp 137-139°C.

Elemental Analysis for C<sub>14</sub>H<sub>8</sub>O<sub>4</sub>

Calculated:     C 70.00, H 3.36;

Found:            C 69.65, H 3.49;

25       M/Z 240 (M+).

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## D. Preparation of 2-hydroxy-4-phenoxyphenylglyoxamide

The compound of part C was combined with 30 mL of concentrated  $\text{NH}_4\text{OH}$  and water, and stirred at room temperature. A homogeneous yellow solution resulted after 30 minutes. The solution was treated with concentrated  $\text{HCl}$  until a tarry residue had formed. The solution was decanted from the residue, and acidified to pH 1 by further addition of concentrated  $\text{HCl}$ . The product was collected by suction filtration and washed with fresh water. A sample was recrystallized with  $\text{EtOAc}$ /hexane for characterization. mp  $144-146^\circ\text{C}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 5.81 (br s, 1H), 6.42 (s, 1H), 6.58 (d,  $J=10.0\text{Hz}$ , 1H), 7.06 (br s, 1H), 7.12 (d,  $J=7.7\text{Hz}$ , 2H), 7.27 (m, 1H), (t,  $J=7.7\text{Hz}$ , 2H), 8.68 (d,  $J=9.2\text{Hz}$ , 1H) M/Z 257 ( $\text{M}^+$ ).

## E. Preparation of 2-(5-carboxypent-1-yloxy)-4-phenoxyphenylglyoxamide methyl ester

2-Hydroxy-4-phenoxyphenylglyoxamide (0.3 g; 1.2 mMol) was added to 60 mg of a 60% suspension of  $\text{NaH}$  in mineral oil in 20 mL of  $\text{DMF}$ . When gas evolution had ceased, 0.3 g of 6-methyl bromohexanate was added. The resultant solution was heated and stirred overnight while immersed in an oil bath maintained at  $60-65^\circ\text{C}$ . The mixture was poured into 100 mL of water and extracted with  $\text{EtOAc}$ . The combined organics were washed with brine, and dried over  $\text{MgSO}_4$ . The product was isolated as a white crystalline solid (0.2 g; 43% yield) by medium pressure chromatography on silica gel, eluting with  $\text{EtOAc}$ /hexane:6/4.

## F. Preparation of 2-(5-carboxypent-1-yloxy)-4-phenoxyphenylglyoxamide

The ester (0.2 g; 0.52 mMol), prepared in step E, above, was combined with 1N  $\text{NaOH}$  (0.52 mL) and 5 mL of methanol in an argon atmosphere. The resultant mixture was stirred at room temperature for 7 days. The solvent

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was removed under reduced pressure. The residual foamy, pale, yellow solid was taken up in water. The aqueous solution was extracted with ethyl acetate, then acidified to pH 1 with concentrated HCl. The product (35 mg; 18% yield) was isolated by suction filtration and washed with fresh water.

Elemental Analysis for C<sub>20</sub>H<sub>21</sub>NO<sub>6</sub>:

Calculated: C 64.68, H 5.70, N 3.77;

10 Found: C 64.50, H 5.72, N 3.65.

M/Z 371 (M+).

#### Example 2

2-(3-carboxyprop-1-yloxy)-4-phenoxyphenylglyoxamide

15

Title compound was prepared as described in Example 1, above. 9% yield. mp 170-172°C.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ: 1.97 (m, 2H), 2.49 (t, J=7.2Hz, 2H), 4.07 (t, J=6.0Hz, 2H), 6.60 (d, J=8.50Hz 1H), 6.83 (s, 1H), 20 7.23 (m, 2H), 7.33 (t, J=7.3Hz, 1H), 7.55 (m, 2H), 7.64 (s, 1H), 7.76 (d, J=8.6Hz, 1H), 8.03 (s, 1H), 12.18 (s, 1H).

M/Z 343 (M+).

25

#### Example 3

2-(6-carboxyhex-1-yloxy)-4-phenoxyphenylglyoxamide

Title compound was prepared as described in Example 30 1, above; 69% yield. mp 132-134°C.

Elemental Analysis for C<sub>21</sub>H<sub>23</sub>NO<sub>6</sub>

Calculated: C 65.44, H 6.02, N 3.63;

Found: C 65.63, H 6.13, N 3.39.

35

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## Example 4

2-(7-carboxyhept-1-yloxy)-4-phenoxyphenylglyoxamide

Title compound was prepared as described in Example  
5 1, above; 24% yield. mp 119-121°C.

Analysis for C<sub>22</sub>H<sub>25</sub>NO<sub>6</sub>

Calculated: C 66.15, H 6.31, N 3.51;

Found: C 65.87, H 6.05, N 3.25.

10

## Example 5

2-(4-carboxybut-1-yloxy)-4-phenoxyphenylglyoxamide

The ester precursor of this acid was prepared by the  
general method outlined in Example 1, steps A-E, above.  
15 The ester (0.193g; 0.52 mMol) was combined with 0.52 mL  
of 1.0N NaOH in 5 mL of methanol under an argon  
atmosphere. The mixture was stirred at room temperature  
for 7 days, then concentrated under reduced pressure to  
give a pale, yellow solid (0.170g; 86% yield).

20

Anal Calcd for C<sub>19</sub>H<sub>18</sub>NO<sub>6</sub>Na·H<sub>2</sub>O:

Calculated: C 57.43, H 5.07, N 3.52;

Found: C 57.43, H 4.91, N 3.08.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ: 1.64 (br s, 4H), 1.90 (br t, 2H), 3.92  
25 (br t, 2H), 6.50 (d, J=8.50Hz 1H), 6.72 (s, 1H), 7.13 (d,  
J=7.3Hz, 2H), 7.23 (t, J=7.3Hz, 1H), 7.46 (t, J=7.3Hz, 2H),  
7.76 (d, J=8.6Hz, 1H), 7.7-8.4 (br s, 2H).

30

## Example 6

Sodium 2-carboxymethoxy-4-phenoxyphenylglyoxamide

A. Preparation of 2-carboxymethoxy-4-  
phenoxyphenylglyoxamide

35

To 25 mL of dry DMF was added 0.54 g (2 mmole) of 2-  
hydroxy-4-phenoxyphenylglyoxamide, the compound of

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Example 1, step D, above, followed by 0.244 mL (2.2 mmole) of methyl bromoacetate, 0.304 g (2.2 mmole) K<sub>2</sub>CO<sub>3</sub>, and 200 mg of dry powdered KI. The mixture was stirred 16 hours at room temperature and evaporated under vacuum. The product was redissolved in EtOAc and washed with brine. The solution was evaporated under vacuum, and the product was purified through chromatography over silica gel (30-40 % EtOAc in hexane), giving 0.461 g (67 %) of 2-carboxymethoxy-4-phenoxyphenylglyoxamide as an oil.

Mass Spectral Analysis (FD) m/z: 343.3 (M<sup>+</sup>)

B. Preparation of sodium 2-carboxymethoxy-4-phenoxyphenylglyoxamide

Into 25 mL of MeOH was dissolved 460 mg (1.34mmole) of the intermediate glyoxamide prepared above. To the stirred solution was added 1.34 mL of 1N NaOH, and the hydrolysis was allowed to continue at room temperature for 24 hours. Solvent was removed under vacuum, leaving behind an oily residue, which, on addition of a few mL of EtOAc, gave 402 mg (89%) of crystalline sodium 2-carboxymethoxy-4-phenoxyphenylglyoxamide, melting at 106°C(d).

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ: 4.12 (s, 3H), 6.57 (d, 1H), 7.09 (d, 2H), 7.21 (t, 1H), 7.43 (t, 2H), 7.58 (d, 2H), 8.16 (br s, 1H)

Example 7

2-(2-carboxy)ethoxy-4-phenoxyphenylglyoxamide

A. Preparation of 2-(1,3-dioxolan-2-yl)ethoxy-4-phenoxyphenylglyoxamide

To a stirred DMF (24 mL) solution containing 0.448 g (1.74mmole) of 2-hydroxy-4-phenoxyphenylglyoxamide, the compound of Example 1, step D, above, was added 0.225 g



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(1.91mmole) of 2-(2-bromoethyl)-1,3-dioxolane, 50 mg of dry powdered KI, and 92 mg (1.91 mmole) of NaH (50% in oil). The mixture was heated at 60°C for 16 hours. The reaction mixture was quenched with cold brine, and the resulting organic layer was washed with cold brine twice. After drying over Na<sub>2</sub>SO<sub>4</sub> and evaporating under vacuum, the product was purified on a preparative silica gel plate (75% EtOAc-25% hexane), giving 220 mg (35%) 2-(1,3-dioxolan-2-yl)ethoxy-4-phenoxyphenylglyoxamide as an oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 2.14 (q, 2H), 3.88-3.98 (m, 4H), 4.12 (t, 2H), 5.08 (t, 1H), 5.51 (bd s, 1H), 6.39 (bd s, 1H), 6.57 (d, 1H), 6.58 (s, 1H), 7.09 (d, 1H), 7.23 (t, 1H), 7.42 (t, 2H), 7.73 (d, 1H)

B. Preparation of 2-(2-carboxyethoxy)-4-phenoxyphenylglyoxamide

In 20 ml of acetone, was dissolved 220 mg (0.62 mmole) of the intermediate dioxolanylglyoxamide prepared above. Jones oxidation reagent was dropped in until the reddish color was not extinguished. Most of the solvent was removed under vacuum, and the reaction mixture was extracted between EtOAc and cold water. The organic layer was shaken with dilute bicarbonate, and the resulting aqueous layer was acidified and extracted with EtOAc. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated under vacuum. The product was redissolved in an acetone-CH<sub>2</sub>Cl<sub>2</sub> solvent mixture (1:1), giving 15 mg (7.4 %) of crystalline 2-carboxyethoxy-4-phenoxyphenylglyoxamide, melting at 140°C (d).

Elemental Analysis for C<sub>17</sub> H<sub>15</sub> N O<sub>6</sub>

Calculated: C, 62.01; H, 4.59; N, 4.25;

Found: C, 61.74; H, 4.64; N, 4.11.



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## Example 8

2-(4-carboxybut-1-yloxy)-4-(2-phenylphenoxy)phenylglyoxamide

5

## A. Preparation of 3-(2-phenylphenoxy)anisole

Into 200 mL of pyridine was added 26.7 g (215 mmoles) of 3-methoxyphenol, 50.0 g (215 mmoles) of 1-bromo-2-phenylbenzene, and 59.3 g (430 mmoles) of K<sub>2</sub>CO<sub>3</sub>. Under argon, the mixture was  
10 heated to 70 °C, and 43.0 g (538 mmoles) powdered CuO was added. The mixture was then heated for 72 hours at reflux with vigorous stirring. After cooling and filtering, the reaction mixture was evaporated under vacuum. The residue was extracted between EtOAc and cold dilute HCl 3 times. The organic layer was dried over  
15 Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated under vacuum. The product was purified via silica gel flash chromatography (0 to 50% EtOAc in hexane), giving 50.9 g (86%) of 3-(2-phenyl)phenoxyanisole as a crystalline solid, melting at 52-54°C.

20 Elemental Analysis for C<sub>19</sub> H<sub>16</sub> O<sub>2</sub>:

Calculated: C, 82.58; H, 5.84; O, 11.58:

Found: C, 82.75; H, 5.88; O, 11.40.

## B. Preparation of 3-(2-phenylphenoxy)phenol

25 To 200 mL HOAc and 80 mL of 40% HBr was added 20 g (72.5 mmoles) of the intermediate anisole prepared above. The mixture was heated 6 hours at reflux. Most of the solvent was removed under vacuum, and the residue was shaken between EtOAc and water. The organic layer was washed with saturated NaHCO<sub>3</sub>, dried over  
30 Na<sub>2</sub>SO<sub>4</sub>, and evaporated under vacuum to give 16 g (85%) of 3-(2-phenyl)phenoxyphenol as an oil, which was used without further purification.

Mass Spectral Analysis (FD) m/z: 262 (M<sup>+</sup>)

35

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C. Preparation of 2-hydroxy-4-(2-phenylphenoxy)phenylglyoxamide

To 50 mL of  $\text{CHCl}_3$  was added 2.62 g (10 mmol) of the intermediate phenol, 100 mg DAP, and 2.1 mL (22 mmol) oxalyl chloride. The mixture was heated at reflux for 16 hours. The solvent was removed under vacuum, giving the oxalyl chloride condensation product as an oil, which was used without further purification.

The oxalyl chloride condensation product (approx. 10 mmol) was dissolved in 25 mL of 1,2-dichloroethane and added over 5 min to 3.99 g (30 mmol)  $\text{AlCl}_3$  dispersed in 25 mL 1,2-dichloroethane cooled in an ice bath. After 2 hours, the ice bath was removed, and the reaction was allowed to continue for 1 hour. The reaction was placed in an ice bath, and 50 mL concentrated  $\text{NH}_4\text{OH}$  was added to it with vigorous stirring. After 1 hour, the reaction was diluted with water and filtered. The filtrate was diluted further with  $\text{CH}_2\text{Cl}_2$  and was shaken in a separatory funnel. The organic layer was washed with cold dilute  $\text{HCl}$ , dried over  $\text{Na}_2\text{SO}_4$ , and evaporated under vacuum. The product was purified over silica gel (first, a 0-100%  $\text{EtOAc}$  in hexane gradient, followed by a 20-80%  $\text{MeOH}$  in  $\text{EtOAc}$ ), giving 206 mg (7.8%) 2-hydroxy-4-(2-phenyl)phenoxyphen-1-yl-glyoxamide. A crystalline analytical sample from  $\text{CH}_2\text{Cl}_2$  melted at 100-103°C. Elemental Analysis For  $\text{C}_{20}\text{H}_{15}\text{N}\text{O}_4$ :

Calculated: C, 72.06; H, 4.54; N, 4.20;

Found: C, 72.26; H, 4.64; N, 3.94.

Mass spectral Analysis (FD)  $m/z$ : 333 ( $\text{M}^+$ )

Also obtained in the latter fractions of the above mentioned chromatography was 1.14 g (34%) of 2-hydroxy-4-(2-phenyl)phenoxyphen-1-yl-glyoxylic acid as a crystalline solid, melting at 205°C (d).

Mass Spectral Analysis (FD)  $m/z$ : 334 ( $\text{M}^+$ )

The glyoxylic acid was converted to the more desired glyoxamide as follows: To 25 mL of  $\text{CH}_2\text{Cl}_2$  was dissolved 0.8 g (2.4 mmol) of the intermediate glyoxylic acid. The mixture was

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cooled by an ice bath, and then a catalytic amount of DMF was added, followed by 0.28 mL (2.9 mmole) of oxalyl chloride. After 1 hour, the ice bath was removed, and the reaction was allowed to warm to room temperature for 1 hour. The solvent was removed under vacuum, and the product was redissolved in 50 mL of  $\text{CH}_2\text{Cl}_2$ . From a lecture bottle,  $\text{NH}_3$  was bubbled in over a 5 minute period with stirring. The reaction was shaken with cold dilute  $\text{HCl}$ , and the organic layer was dried over  $\text{Na}_2\text{SO}_4$ , and evaporated under vacuum. The crude product crystallized from  $\text{CH}_2\text{Cl}_2$ -hexane, giving an additional 303 mg (38%) of 2-hydroxy-4-(2-phenyl)phenoxyphenylglyoxamide. (17%), mp =100-103°C. Mass Spectral Analysis (FD) m/z: 333 ( $\text{M}^+$ )

D. Preparation of 2-(4-carboxymethoxybut-1-yloxy)-4-(2-phenyl)phenoxyphenylglyoxamide

To 62.4 mg (1.3 mmole) of 50%  $\text{NaH}$  in mineral oil, which had been washed with hexane, was added 50 mL of dry DMF, 0.40 g (1.2 mmole) of 2-hydroxy-4-(2-phenyl)phenoxyphenylglyoxamide, and 100 mg of powdered dry  $\text{KI}$  and 4-methyl bromobutanoate. The reaction mixture was stirred and heated 16 hours at 60°C, quenched with dilute cold  $\text{HCl}$ , and after diluting further with cold brine, it was extracted with  $\text{EtOAc}$ . The organic layer was washed with acidified brine twice, dried over  $\text{Na}_2\text{SO}_4$ , evaporated under vacuum. When chromatographed over silica gel (20 to 80%  $\text{EtOAc}$  in hexane), 254 mg (47%) 2-(4-carboxymethoxy)butoxy-4-(2-phenyl)phenoxyphenylglyoxamide was prepared as an oil.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.7 -1.9 (m, 4H), 2.39 (t, 2H), 3.69 (s, 3H), 3.93 (t, 2H), 5.84 (br s, 1H), 6.29 (br s, 1H), 6.46 (s, 1H), 6.49 (d, 1H), 7.12 (d, 1H), 7.3 -7.5 (m, 8H), 7.65 (d, 1H);

Mass Spectral Analysis (FD) m/z: 447 ( $\text{M}^+$ ).

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E. Preparation of 2-(4-carboxybut-1-yloxy)-4-(2-phenyl)phenoxyphenylglyoxamide

Into 10 mL of MeOH was dissolved with stirring, 254 mg (0.57 mmole) of the carbomethoxy intermediate prepared above, followed by the addition of 1.14 mL 0.5 N NaOH. The mixture was stirred 16 hours at room temperature. Solvent was removed under vacuum, and the residue was diluted with water and extracted with 4:1 EtOAc: hexane. The aqueous layer was acidified with dilute HCl, and shaken with EtOAc. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated under vacuum. Crystalline 2-(4-carboxy)butoxy-4-(2-phenyl)phenoxyphenylglyoxamide was obtained, 181 mg (73%), melting at MP = 118-20°C

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Elemental Analysis for C<sub>25</sub> H<sub>23</sub> N O<sub>6</sub>:

Calculated: C, 68.95; H, 5.79; N, 3.23;

Found: C, 68.91; H, 5.58; N, 3.22;

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ: 1.7 - 1.9 (m, 4H), 2.37 (t, 2H), 3.93

5 (t, 2H), 6.32 (br s, 1H), 6.44 (s, 1H), 6.45 (d, 1H), 6.47

(br s, 1H), 7.12 (d, 1H), 7.3 - 7.5 (m, 8H), 7.65 (d, 1H);

Mass Spectral Analysis (FD) m/z: 433 (M<sup>+</sup>).

### Example 9

10

#### Sodium 2-(4-carboxybut-1-yloxy)-4-phenoxy-5-methylphenyglyoxamide

##### A. Preparation of 3-hydroxy-4-methylanisole

15

To a solution of 10.0 g (65.8 mmols) of 2-hydroxy-4-methoxybenzaldehyde in 50 mL of HOAc and 50 mL of concentrated HCl, was added 17.2 g (263.2 mg atoms) of powdered zinc. The mixture was heated one hour at 85-90°C and then extracted three times between EtOAc and

20 saturated NaCl solution. The organic layer was washed with saturated NaHCO<sub>3</sub>, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated under vacuum. The crude product was purified via silica gel flash chromatography (0 to 20% EtOAc in hexane), giving 2.0 g (22.0%) of 3-hydroxy-4-methylanisole as an

25 oil which crystallized on standing, melting at 34-35°C.

##### B. Preparation of 4-methyl-3-phenoxyanisole

Into 50 mL pyridine, was added 4.14 g (30 mmols) of the hydroxyanisole prepared above, 3.48 mL (33 mmols) of

30 bromobenzene, and 4.8 g (60 mmols) of K<sub>2</sub>CO<sub>3</sub>. Under argon, the mixture was heated to 70°C, and 4.8 g (60 mmols) of powdered CuO was added. The mixture was then heated for 16 hours at reflux with vigorous stirring. Additional CuO (4.8 g, 60 mmols) and bromobenzene (3.5

35 mL, 60 mmols) were added, and the reaction mixture was heated 16 hours at reflux. After cooling and filtering,

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the reaction mixture

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was evaporated under vacuum. The residue was extracted between EtOAc and cold dilute HCl three times. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated under vacuum. The product was purified via silica gel flash chromatography (0 to 30% EtOAc in hexane), giving 3.32 g (51.7%) 4-methyl-3-phenoxyanisole as an oil.

C. Preparation of 4-methyl-3-phenoxyphenol

10 To 50 mL of HOAc and 20 mL of 40% HBr was added 3.2 g (15.0 mmoles) of the intermediate methylanisole prepared above, and the mixture was heated 16 hours at reflux. Most of the solvent was removed under vacuum and the residue was shaken between EtOAc and water. The product, after drying over MgSO<sub>4</sub> and evaporating under vacuum, was purified via silica gel flash chromatography (0-30% EtOAc in hexane), giving 1.81 g (60 %) 4-methyl-3-phenoxyphenol as an oil.



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D. Preparation of 2-hydroxy-5-methyl-4-phenoxyphenylglyoxylic acid

To 100mL of  $\text{CHCl}_3$  was added 1.70 g (8.5 mmol) of the intermediate methylphenol prepared above, 30 mg of DAP, and 1.79 mL (18.7 mmol) of oxalyl chloride. The mixture was heated at reflux for 16 hours. The solvent was removed under vacuum, giving the oxalyl chloride condensation product as an oil, which was used without purification. The intermediate oxalyl chloride product was dissolved in 25mL of 1,2-dichloroethane and added over 5 minutes to 3.39 g (25.5 mmol) of  $\text{AlCl}_3$  dispersed in 100mL of 1,2-dichloroethane cooled in an ice bath. After 1 hour, the ice bath was removed and the reaction was allowed to continue for 30 minutes. The reaction mixture was poured into 300 mL of a 3:1 mixture of crushed ice and concentrated  $\text{HCl}$  with vigorous stirring. The organic layer was separated and washed with cold dilute  $\text{HCl}$  and dilute  $\text{K}_2\text{CO}_3$ . The carbonate extract was acidified with dilute  $\text{HCl}$  and extracted with  $\text{EtOAc}$ . After drying over  $\text{MgSO}_4$  and evaporating under vacuum, 1.04 g (45%) of 2-hydroxy-5-methyl-4-phenoxyphenylglyoxylic acid as a crystalline solid was obtained, melting at 85-87°C.

E. Preparation of 2-hydroxy-5-methyl-4-phenoxyphenylglyoxamide

To 25 mL of  $\text{CH}_2\text{Cl}_2$  containing a few drops of DMF, was added 0.80 g (4 mmol) of the glyoxylic acid intermediate prepared above. The mixture was cooled in an ice bath, and 0.46 mL of oxalyl chloride (4.8 mmol) was added. After 1 hour, the ice bath was removed and the reaction was allowed to continue for 1 hour. The solvent and excess oxalyl chloride were removed under vacuum, and the product was redissolved in 50mL of  $\text{CH}_2\text{Cl}_2$  and cooled in an ice bath. Approximately 5 mL of liquid  $\text{NH}_3$  was added, and the reaction was stirred for 1 hour. The reaction mixture was quenched with cold concentrated



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HCl and, after diluting with brine and CH<sub>2</sub>Cl<sub>2</sub>, it was shaken in a separatory funnel. The organic layer was washed with brine, dried over MgSO<sub>4</sub>, and concentrated, giving 225 mg (21 %) of 2-hydroxy-5-methyl-4-phenoxyphenylglyoxamide, melting at 158-60°C.

Elemental Analysis for C<sub>15</sub>H<sub>13</sub>NO<sub>4</sub>:

Calculated: C, 66.42; H, 4.83; N, 5.16;

Found: C, 66.04; H, 4.75; N, 4.82.

10

F. Preparation of 2-(4-carboxymethoxybut-1-yloxy)-4-phenoxy-5-methylphenylglyoxamide

Compound was prepared as described in Example 8, step D, above.

15 Yield = 47%, oil

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.2-1.8 (m, 4H), 2.23 (s, 3H), 2.35 (t, 2H), 3.66 (s, 3H), 3.81 (t, 2H), 6.11 (br s, 1H), 6.34 (s, 1H), 6.40 (br s, 1H), 7.01 (d, 2H), 7.17 (t, 1H),  
20 7.38 (t, 2H), 7.64 (s, 1H)

G. Preparation of sodium 2-(4-carboxybut-1-yloxy)-4-phenoxy-5-methylphenylglyoxamide

Title compound was prepared as described in Example 8, step D, above.

25 Yield = 70%, MP = 206-9°C

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ: 1.5-1.6 (m, 4H), 1.86 (t, 2H), 2.17 (s, 4H), 3.78 (t, 2H), 6.52 (s, 1H), 7.04 (d, 2H), 7.18 (t, 1H), 7.43 (t, 2H), 7.64 (s, 1H), 7.83 (br s, 1H),  
30 7.40 (br s, 1H).

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## Example 10

2-(3-(disodium phosphonoyl)prop-1-yloxy)-4-  
phenoxyphenylglyoxamide5 A. Preparation of 2-(3-dimethoxyphosphono)prop-1-yloxy-  
4-phenoxyphenylglyoxamide

To 20 mL of dry DMF was added with stirring, 0.457 g (1.78 mmole) of 2-hydroxy-4-phenoxyphenylglyoxamide, 0.411 g (1.78 mmole) of (3-bromoprop-1-yl)dimethylphosphonate, 100 mg of dry powdered KI, and 57 mg (1.78 mmole) of 50% NaH dispersion in mineral oil. The mixture was heated 16 hours at 6°C, cooled, quenched with cold dilute HCl, and shaken between EtOAc and brine. The organic layer was washed with brine twice, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated under vacuum. The product was chromatographed over silica gel (0 to 100% EtOAc in hexane), giving 0.353 g (49%) 2-(3-dimethoxyphosphonoyl)prop-1-yloxy-4-phenoxyphenylglyoxamide as an oil.

20

Elemental Analysis for C<sub>19</sub> H<sub>22</sub> N O<sub>7</sub>:

Calculated: C, 56.02; H, 5.73; N, 2.67;

Found: C, 56.02; H, 5.44; N, 2.67;

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 2.0 - 2.2 (m, 4H), 3.77 (s, 3H), 3.81 (s, 3H), 4.00 (t, 2H), 6.25 (br s, 1H), 6.56 (s, 1H), 6.59 (d, 1H), 7.09 (d, 2H), 7.23 (t, 1H), 7.40 (t, 2H), 7.78 (d, 1H);

Mass Spectral Analysis (FD) m/z: 407.

## 30 B. Preparation of 2-(3-(disodium phosphonoyl)prop-1-yloxy)-4-phenoxyphenylglyoxamide

Into 10 mL of CH<sub>2</sub>Cl<sub>2</sub>, was added 0.35 g of intermediate dimethylphosphonate prepared above, 0.95 g (6.88 mmole) of K<sub>2</sub>CO<sub>3</sub>, and 0.91 mL (6.88 mmole) of trimethylsilyl bromide. The reaction mixture was stirred 16 hours at room temperature. The reaction mixture was evaporated under vacuum, and treated with 15 mL of MeOH

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at room temperature for 1 hour. The mixture was filtered and diluted with EtOAc to give a solid, which was chromatographed on an ionization column (5- 30% acetonitrile in water). Fractions were lyophilized, giving 140 mg (43%) of 2-(3-disodium phosphonoyl)prop-1-yloxy-4-phenoxyphenylglyoxamide as a solid.

$^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$ : 1.73 (m, 2H), 2.17 (m, 2H), 4.10 (t, 2H), 6.63 (d, 1H), 6.75 (s, 1H), 7.19 (d, 2H), 7.32 (t, 1H), 7.53 (t, 2H), 7.84 (d, 1H).

#### Example 11

2-(4-carboxybut-1-yloxy)-4-(3-phenylphenoxy)phenylglyoxamide

15

##### A. Preparation of 3-(3-phenylphenoxy)anisole

Under the Ullmann conditions used in Example 8, steps A and B, above, 13.3 g of 3-methoxyphenol (107 mmole) was condensed with 1-bromo-3-phenylbenzene, giving, after purifying over silica gel, (0-30% EtOAc in hexane gradient) 17.8 g (60 %) of 3-(3-phenylphenoxy)anisole as a crystalline solid, melting at 41-42°C.

25 Mass Spectral Analysis (FD)  $m/z$ : 276 ( $M^+$ )

##### B. Preparation of 3-(3-phenylphenoxy)phenol

The anisole derivative prepared above (17.7 g, 64 mmole) was demethylated in HOAc/40% HBr under the conditions of Example 8, step C, above and, after purifying the product over silica gel, (0-30% EtOAc in hexane gradient), 12.2 g (72%) of 3-(3-phenylphenoxy)phenol as an oil was obtained.

35 Elemental Analysis for  $C_{18}H_{14}O_2$  :

Calculated: C, 82.42; H, 5.38; O, 12.20;

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Found: C, 82.17; H, 5.38; O, 12.42;

C. Preparation of 2-hydroxy-4-(3-phenylphenoxy)phenylglyoxylic acid

5 As in Example 8, step D, above, the intermediate phenol prepared above (7.4 g, 31.4 mmole) was treated with oxalyl chloride, and after removing solvent, the product was subjected to  $\text{AlCl}_3$ . The reaction mixture was quenched by pouring it into 1L of 2:1 mixture of crushed  
10 ice and concentrated HCl with vigorous stirring. The organic layer was separated, washed with brine, diluted with EtOAc to achieve a clear solution, and dried over  $\text{MgSO}_4$ . The product was concentrated under vacuum and purified by chromatography over silica gel (0-100 % EtOAc  
15 in hexane then 0-20% MeOH in EtOAc), giving 4.3 g (42%) 2-hydroxy-4-(3-phenylphenoxy)phenylglyoxylic acid as an oil.

Mass Spectral Analysis (FD)  $m/z$ : 334 ( $\text{M}^+$ )

20

D. Preparation of 2-hydroxy-4-(3-phenylphenoxy)phenylglyoxylic acid lactone

Into 150 mL of  $\text{CH}_2\text{Cl}_2$  was dissolved 4.3 g (12.9 mmole) of the glyoxylic acid prepared above. After  
25 adding 10 drops of DMF and cooling the mixture with an ice bath, 1.48 mL of oxalyl chloride (15.5 mmole) was added to the stirred mixture in one portion. After 30 minutes the ice bath was removed, and the reaction was allowed to continue for 1 hour. The reaction mixture was  
30 concentrated under vacuum and a solid formed, which was washed with 1:1  $\text{CH}_2\text{Cl}_2$ :hexane, giving 3.5 g 2-hydroxy-4-(3-phenylphenoxy)phenylglyoxylic acid lactone, melting at 55-58°C.

35 Mass Spectral Analysis (FD)  $m/z$ : 316 ( $\text{M}^+$ )

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E. Preparation of 2-(4-carboxymethoxybut-1-yloxy)-4-(3-phenylphenoxy)phenylglyoxamide

To 50 mL of dry DMF, was added 1.58 g (5 mmole) of 2-hydroxy-4-(3-phenylphenoxy)phenylglyoxylic acid lactone with stirring. The solution was cooled with an ice bath and 0.234 g (6.0 mmole) of sodium amide was added. After 15 minutes, 0.786 mL (5.5 mmole) of methyl 5-bromovalerate was added, and the ice bath was removed, allowing the mixture to attain room temperature. The mixture was heated 16 hours at 60°C and then quenched with cold dilute HCl. The reaction mixture was shaken between EtOAc and cold dilute HCl. The organic layer was washed with cold dilute HCl twice, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under vacuum. Product was chromatographed over silica gel (0 to 70% EtOAc in hexane), giving 0.682 g (31%) 2-(4-carboxymethoxybut-1-yloxy)-4-(3-phenylphenoxy)phenylglyoxamide as an oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.8-1.9 (m, 4H), 2.40 (t, 2H), 3.6 (s, 3H), 4.00 (t, 2H), 5.77 (br s, 1H), 6.30 (br s, 1H), 6.60 (s, 1H), 6.61 (d, 1H), 7.06 (br s, 1H) 7.3-7.5 (m, 6H), 7.59 (d, 2H), 7.74 (d, 1H).

F. Preparation of 2-(4-carboxybut-1-yloxy)-4-(3-phenyl)phenoxyphenylglyoxamide

Into 20 mL of MeOH was dissolved at room temperature, 0.682 g (1.53 mmole) of the glyoxamide intermediate prepared above. To the solution was added 3.05 mL of 0.5 N NaOH. After stirring for 15 hours, the solvent was removed under vacuum, and the residue was diluted with water and extracted with EtOAc. Crystals were filtered from the organic layer, giving 0.458 g (69%) of 2-(4-carboxy)butoxy-4-(3-phenyl)phenoxyphenylglyoxamide, melting at 97-98°C.

35

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$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.6-1.8 (m, 4H), 2.28 (t, 2H), 4.02 (t, 2H), 6.61 (d, 1H), 6.86 (s, 1H), 7.15 (br s, 1H), 7.4-7.6 (m, 7H), 7.70 (d, 3H), 7.94 (br s, 1H), 12.02 (br s, 1H);  
Mass Spectral Analysis (FD)  $m/z$ : 433 ( $\text{M}^+$ ).

5

## Example 12

2-(4-carboxypent-1-yloxy)-4-(2-phenylphenoxy)phenylglyoxamide

10

A. Preparation of 2-(4-carbomethoxypent-1-yloxy)-4-(2-phenylphenoxy)phenylglyoxamide

Compound was prepared as described in Example 8, steps A-D, above.

15 Yield = 63%, MP = 70 - 74°C

Elemental Analysis for  $\text{C}_{27}\text{H}_{27}\text{N}\text{O}_6$ :

Calculated: C, 70.27; H, 5.90; N, 3.04;

Found: C, 72.26; H, 6.31; N, 2.95;

20 Mass Spectral Analysis (FD)  $m/z$ : 461 ( $\text{M}^+$ ).

B. Preparation of 2-(4-carboxy)pentoxy-4-(2-phenyl)phenoxyphenylglyoxamide

25 Title compound was prepared as described in Example 8, step E above.

Yield = 42%, MP = 97 - 99°C

Elemental Analysis for  $\text{C}_{26}\text{H}_{25}\text{N}\text{O}_6$ :

Calculated: C, 69.79; H, 5.53; N, 3.13;

30 Found: C, 69.57; H, 5.62; N, 3.06;

$^1\text{H}$  NMR ( $\text{DMSO-d}_6$ )  $\delta$ : 1.39 (quin, 2H), 1.48 (quint, 2H), 1.63 (quint, 2H), 2.21 (t, 2H), 3.88 (t, 2H), 6.41 (d, 1H), 6.63 (s, 1H), 7.17 (d, 1H), 7.3 - 7.6 (m, 8H), 7.88 (s, 1H);

35 Mass Spectral Analysis (FD)  $m/z$ : 447 ( $\text{M}^+$ ).

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## Example 13

## 2-(4-carboxybut-1-yloxy)-4-phenylphenylglyoxamide

## 5 A. Preparation of 2-hydroxy-4-phenylphenylglyoxylic acid lactone

Commercially available 3-phenylphenol was treated with oxalyl chloride, and the resulting product was treated with  $\text{AlCl}_3$  as described in Example 1, step C, 10 above. After quenching the reaction mixture from the  $\text{AlCl}_3$  treatment with water, it was dried over  $\text{MgSO}_4$  and concentrated, giving crystalline 2-hydroxy-4-phenylphenylglyoxylic acid lactone (85%), melting at 131-33°C.

15

Mass Spectral Analysis (FD)  $m/z$ : 224 ( $\text{M}^+$ )

## B. Preparation of 2-hydroxy-4-phenylphenylglyoxamide

The lactone prepared above, (4.0 g, 17.9 mmole), was 20 dissolved in 200 mL of  $\text{CH}_2\text{Cl}_2$  and excess gaseous ammonia was bubbled in over 5 minutes. The reaction mixture was shaken with brine, dried over  $\text{MgSO}_4$ , and concentrated. On cooling, the product crystallized, giving 2-hydroxy-4-phenylphenylglyoxamide (93%), with a mp of 150°C (d).

25

Elemental Analysis for  $\text{C}_{14}\text{H}_{11}\text{O}_3$ :

Calculated: C, 69.70; H, 4.60; N, 5.81;

Found: C, 69.72; H, 4.59; N, 5.57.

Mass Spectral Analysis (FD)  $m/z$ : 241 ( $\text{M}^+$ )

30

## C. Preparation of 2-(4-carboxymethoxybut-1-yloxy)-4-phenylphenylglyoxamide

Compound was prepared as described in Example 8, step D, above.

35 Yield = 28%, MP = 119 - 20°C



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$^1\text{H}$  NMR ( $\text{DMSO-d}_6$ )  $\delta$ : 1.6 - 1.8 (m, 4H), 2.39 (t, 2H), 3.58 (s, 3H), 4.18 (t, 2H), 7.36 (d, 1H), 7.38 (s, 1H), 7.4 - 7.5 (m, 3H), 7.58 (s, 1H), 7.70 (d, 1H), 7.38 (d, 2H), 8.00 (s, 1H);

5 Mass Spectral Analysis (FD)  $m/z$ : 355 ( $\text{M}^+$ ).

D. Preparation of 2-[(4-carboxybut-1-yloxy)-4-phenylphenylglyoxamide

Title compound was prepared as described in Example  
10 8, step E, above.

Yield = 58%, MP = 157-158°C

Elemental Analysis for  $\text{C}_{19}\text{H}_{19}\text{N}_5\text{O}_5$ :

Calculated: C, 66.85; H, 5.61; N, 4.10;

Found: C, 66.81; H, 5.59; N, 4.14;

15  $^1\text{H}$  NMR ( $\text{DMSO-d}_6$ )  $\delta$ : 1.6 - 1.8 (m, 4H), 2.32 (t, 2H), 4.14 (t, 2H), 7.36 (d, 1H), 7.39 (s, 1H), 7.4 - 7.5 (m, 3H), 7.56 (s, 1H), 7.71 (d, 1H), 7.78 (d, 1H), 8.00 (s, 1H), 12.02 (s, 1H);

Mass Spectral Analysis (FD)  $m/z$ : 341 ( $\text{M}^+$ ).

20

Therapeutic Use of Phenyl Glyoxamides

The phenyl glyoxamide compounds described  
25 herein are believed to achieve their beneficial therapeutic action principally by direct inhibition of human sPLA<sub>2</sub>, and not by acting as antagonists for arachidonic acid, nor other active agents below arachidonic acid in the arachidonic acid cascade, such as  
30 5-lipoxygenases, cyclooxygenases, etc.

The method of the invention for inhibiting sPLA<sub>2</sub> mediated release of fatty acids comprises contacting sPLA<sub>2</sub> with a therapeutically effective amount of the compound of Formula (I), or salts thereof.

35 The compounds of the invention may be used in a method of treating a mammal (e.g., a human) to alleviate



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the pathological effects of septic shock, adult respiratory distress syndrome, pancreatitis, trauma, bronchial asthma, allergic rhinitis, and rheumatoid arthritis; wherein the method comprises administering to the mammal a compound of formula (I) in a therapeutically effective amount. A "therapeutically effective" amount is an amount sufficient to inhibit sPLA<sub>2</sub> mediated release of fatty acid and to thereby inhibit or prevent the arachidonic acid cascade and its deleterious products.

The therapeutic amount of compound of the invention needed to inhibit sPLA<sub>2</sub> may be readily determined by taking a sample of body fluid and assaying it for sPLA<sub>2</sub> content by conventional methods.

#### Pharmaceutical Formulations of the Invention

As previously noted the compounds of this invention are useful for inhibiting sPLA<sub>2</sub> mediated release of fatty acids such as arachidonic acid. By the term, "inhibiting" is meant the prevention or therapeutically significant reduction in release of sPLA<sub>2</sub> initiated fatty acids by the compounds of the invention. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

In general, the compounds of the invention are most desirably administered at a concentration that will generally afford effective results without causing any serious side effects and can be administered either as a single unit dose, or if desired, the dosage may be divided into convenient subunits administered at suitable times throughout the day.

The specific dose of a compound administered according to this invention to obtain therapeutic or prophylactic effects will, of course, be determined by the particular circumstances surrounding the case,

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including; for example, the route of administration, the age, weight and response of the individual patient, the condition being treated and the severity of the patient's symptoms. Typical daily doses will contain a non-toxic dosage level of from about 0.01 mg/kg to about 50 mg/kg of body weight of an active compound of this invention.

Preferably the pharmaceutical formulation is in unit dosage form. The unit dosage form can be a capsule or tablet itself, or the appropriate number of any of these. The quantity of active ingredient in a unit dose of composition may be varied or adjusted from about 0.1 to about 1000 milligrams or more according to the particular treatment involved. It may be appreciated that it may be necessary to make routine variations to the dosage depending on the age and condition of the patient. The dosage will also depend on the route of administration.

A "chronic" condition means a deteriorating condition of slow progress and long continuance. As such, it is treated when it is diagnosed and continued throughout the course of the disease. An "acute" condition is an exacerbation of short course followed by a period of remission. In an acute event, compound is administered at the onset of symptoms and discontinued when the symptoms disappear.

Pancreatitis, trauma-induced shock, bronchial asthma, allergic rhinitis and rheumatoid arthritis may occur as an acute event or a chronic event. Thus, the treatment of these conditions contemplates both acute and chronic forms. Septic shock and adult respiratory distress, on the other hand, are acute conditions treated when diagnosed.

The compound can be administered by a variety of routes including oral, aerosol, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal.

Pharmaceutical formulations of the invention are prepared by combining (e.g., mixing) a

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therapeutically effective amount of the phenyl glyoxamide compounds of the invention together with a pharmaceutically acceptable carrier or diluent therefor. The present pharmaceutical formulations are prepared by known procedures using well known and readily available ingredients.

In making the compositions of the present invention, the active ingredient will usually be admixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semi-solid or liquid material which acts as a vehicle, or can be in the form of tablets, pills, powders, lozenges, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), or ointment, containing, for example, up to 10% by weight of the active compound. The compounds of the present invention are preferably formulated prior to administration.

For the pharmaceutical formulations any suitable carrier known in the art can be used. In such a formulation, the carrier may be a solid, liquid, or mixture of a solid and a liquid. Solid form formulations include powders, tablets and capsules. A solid carrier can be one or more substances which may also act as flavoring agents, lubricants, solubilisers, suspending agents, binders, tablet disintegrating agents and encapsulating material.

Tablets for oral administration may contain suitable excipients such as calcium carbonate, sodium carbonate, lactose, calcium phosphate, together with disintegrating agents, such as maize, starch, or alginic acid, and/or binding agents, for example, gelatin or acacia, and lubricating agents such as magnesium stearate, stearic acid, or talc.

In powders the carrier is a finely divided solid which is in admixture with the finely divided

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active ingredient. In tablets the active ingredient is mixed with a carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets  
5 preferably contain from about 1 to about 99 weight percent of the active ingredient which is the novel compound of this invention. Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar lactose, pectin, dextrin, starch, gelatin, tragacanth,  
10 methyl cellulose, sodium carboxymethyl cellulose, low melting waxes, and cocoa butter.

Sterile liquid form formulations include suspensions, emulsions, syrups and elixirs.

The active ingredient can be dissolved or  
15 suspended in a pharmaceutically acceptable carrier, such as sterile water, sterile organic solvent or a mixture of both. The active ingredient can often be dissolved in a suitable organic solvent, for instance aqueous propylene glycol. Other compositions can be made by dispersing the  
20 finely divided active ingredient in aqueous starch or sodium carboxymethyl cellulose solution or in a suitable oil.

The following pharmaceutical formulations 1 through 8 are illustrative only and are not intended to  
25 limit the scope of the invention in any way. "Active ingredient", refers to a compound according to Formula (I) or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

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Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

	Quantity <u>(mg/capsule)</u>
2-(6-carboxyhex-1-yloxy)-4- phenoxyphenyl-5- ethylphenylglyoxamide	250
Starch, dried	200
Magnesium stearate	<u>10</u>
Total	460 mg

5

Formulation 2

A tablet is prepared using the ingredients below:

	Quantity <u>(mg/tablet)</u>
2-(4-carboxybut-1-yloxy)-4-(3,5- diphenyl)phenyl)-6- methylphenylglyoxamide	250
Cellulose, microcrystalline	400
Silicon dioxide, fumed	10
Stearic acid	<u>5</u>
Total	665 mg

10

The components are blended and compressed to form tablets each weighing 665 mg

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Formulation 3

An aerosol solution is prepared containing the following components:

	<u>Weight</u>
2-(2-carboxyethoxy)-4-(3-(3-fluorophenyl)benzyl-6-butylphenylglyoxamide	0.25
Ethanol	25.75
Propellant 22 (Chlorodifluoromethane)	<u>74.00</u>
Total	100.00

5

The active compound is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to -30°C and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted with the remainder of the propellant. The valve units are then fitted to the container.

10

Formulation 4

15

Tablets, each containing 60 mg of active ingredient, are made as follows:

2-(diethoxyphosphonoyl)methoxy-4-benzylphenylglyoxamide	60 mg
Starch	45 mg
Microcrystalline cellulose	35 mg
Polyvinylpyrrolidone (as 10% solution in water)	4 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	<u>1 mg</u>
Total	150 mg

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The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The aqueous solution containing polyvinylpyrrolidone is mixed with the resultant powder, and the mixture then is passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

#### Formulation 5

Capsules, each containing 80 mg of active ingredient, are made as follows:

2-(4-phosphonoylbut-1-yloxy)-4-(2,6-dimethoxy)phenylphenylglyoxamide	80 mg
Starch	59 mg
Microcrystalline cellulose	59 mg
Magnesium stearate	<u>2 mg</u>
Total	200 mg

The active ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules in 200 mg quantities.



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Formulation 6

Suppositories, each containing 225 mg of active ingredient, are made as follows:

2-(4-methoxysulfonylbut-1-yloxy)-4-(4-propyl)benzyl-5-methylphenylglyoxamide	225 mg
Saturated fatty acid glycerides	<u>2,000 mg</u>
Total	2,225 mg

5

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.

10

Formulation 7

Suspensions, each containing 50 mg of active ingredient per 5 ml dose, are made as follows:

15

2-(3-methoxycarbonylprop-1-yloxy)-4-(4-phenyl)benzylphenylglyoxamide	50 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 ml
Benzoic acid solution	0.10 ml
Flavor	q.v.
Color	q.v.
Purified water to total	5 ml

20

The active ingredient is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color are diluted with a portion of the water and added, with stirring. Sufficient water is then added to produce the required volume.

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Formulation 8

An intravenous formulation may be prepared as follows:

5

2-carbomethoxymethoxy-4-phenyl-5- 100 mg  
fluoro-6-methylphenylglyoxamide

Isotonic saline 1,000 ml

The solution of the above ingredients generally is administered intravenously to a subject at a rate of 1 ml per minute.

10

Assay ExperimentsAssay Example 1

15

The following chromogenic assay procedure was used to identify and evaluate inhibitors of recombinant human secreted phospholipase A<sub>2</sub>. The assay described herein has been adapted for high volume screening using 96 well microtiter plates. A general description of this assay method is found in the article, "Analysis of Human Synovial Fluid Phospholipase A<sub>2</sub> on Short Chain Phosphatidylcholine-Mixed Micelles: Development of a Spectrophotometric Assay Suitable for a Microtiterplate Reader", by Laure J. Reynolds, Lori L. Hughes, and Edward A. Dennis, Analytical Biochemistry, 204, pp. 190-197, 1992 (the disclosure of which is incorporated herein by reference):

20

25

Reagents:

REACTION BUFFER -

30

CaCl<sub>2</sub>·2H<sub>2</sub>O (1.47 g/L)

KCl (7.455 g/L)

Bovine Serum Albumin (fatty acid free) (1 g/L)

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(Sigma A-7030, product of Sigma Chemical  
Co. St. Louis MO, USA)

TRIS HCl (3.94 g/L)

pH 7.5 (adjust with NaOH)

5 ENZYME BUFFER -

0.05 NaOAc.3H<sub>2</sub>O, pH 4.5

0.2 NaCl

Adjust pH to 4.5 with acetic acid

DTNB - 5,5'-dithiobis-2-nitrobenzoic acid

10 RACEMIC DIHEPTANOYL THIO - PC

racemic 1,2-bis(heptanoylthio)-1,2-dideoxy-sn-  
glycero-3-phosphorylcholine

TRITON X-100<sup>TM</sup> prepare at 6.249 mg/ml in  
reaction buffer to equal 10uM.

15 TRITON X-100<sup>TM</sup> is a polyoxyethylene non-ionic  
detergent supplied by

Pierce Chemical Company

3747 N. Meridian Road

Rockford, Illinois 61101

20 REACTION MIXTURE -

A measured volume of racemic dipheptanoyl thio  
PC supplied in chloroform at a concentration of 100 mg/ml  
is taken to dryness and redissolved in 10 millimolar  
TRITON X-100<sup>TM</sup> nonionic detergent aqueous solution.

25 Reaction Buffer is added to the solution, then DTNB to  
give the Reaction Mixture.

The reaction mixture thus obtained contains 1mM  
diheptanoly thio-PC substrate, 0.29 mM Triton X-100<sup>TM</sup>  
detergent, and 0.12 mM DTMB in a buffered aqueous  
30 solution at pH 7.5.

Assay Procedure:

1. Add 0.2 ml reaction mixture to all wells;
2. Add 10 ul test compound (or solvent blank) to  
35 appropriate wells, mix 20 seconds;
3. Add 50 nanograms of SPLA<sub>2</sub> (10 microliters) to  
appropriate wells;

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4. Incubate plate at 40°C for 30 minutes;

5. Read absorbance of wells at 405 nanometers with an automatic plate reader.

All compounds were tested in triplicate.

5 Typically, compounds were tested at a final concentration of 5 ug/ml. Compounds were considered active when they exhibited 40% inhibition or greater compared to uninhibited control reactions when measured at 405 nanometers. Lack of color development at 405 nanometers  
10 evidenced inhibition. Compounds initially found to be active were reassayed to confirm their activity and, if sufficiently active, IC<sub>50</sub> values were determined. Typically, the IC<sub>50</sub> values (see, Table I, below) were determined by diluting test compound serially two-fold  
15 such that the final concentration in the reaction ranged from 45 ug/mL to 0.35 ug/ml. More potent inhibitors required significantly greater dilution. In all cases, % inhibition measured at 405 nanometers generated by enzyme reactions containing inhibitors relative to the  
20 uninhibited control reactions was determined. Each sample was titrated in triplicate and result values were averaged for plotting and calculation of IC<sub>50</sub> values. IC<sub>50</sub> were determined by plotting log concentration versus inhibition values in the range from 10-90% inhibition.  
25 Compounds of the instant invention were tested in Assay Example 1 and were found to be effective.

#### Assay Example 2

##### Method:

30 Male Hartley strain guinea pigs (500-700g) were killed by cervical dislocation and their heart and lungs removed intact and placed in aerated (95% O<sub>2</sub>:5% CO<sub>2</sub>) Krebs buffer. Dorsal pleural strips (4x1x25mm) were dissected from intact parenchymal segments (8x4x25mm) cut  
35 parallel to the outer edge of the lower lung lobes. Two adjacent pleural strips, obtained from a single lobe and representing a single tissue sample, were tied at either

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end and independently attached to a metal support rod. One rod was attached to a Grass force-displacement transducer Model FTO3C, product of Grass Medical Instruments Co., Quincy, MA, USA). Changes in isometric tension were displayed on a monitor and thermal recorder (product of Modular Instruments, Malvern, PA). All tissues were placed in 10 ml jacketed tissue baths maintained at 37°C. The tissue baths were continuously aerated and contained a modified Krebs solution of the following composition (millimolar) NaCl, 118.2; KCl, 4.6; CaCl<sub>2</sub>·2H<sub>2</sub>O, 2.5; MgSO<sub>4</sub>·7H<sub>2</sub>O, 1.2; NaHCO<sub>3</sub>, 24.8; KH<sub>2</sub>PO<sub>4</sub>, 1.0; and dextrose, 10.0. Pleural strips from the opposite lobes of the lung were used for paired experiments. Preliminary data generated from tension/response curves demonstrated that resting tension of 800mg was optimal. The tissues were allowed to equilibrate for 45 min. as the bath fluid was changed periodically.

20 Cumulative concentration-response curves:

Initially tissues were challenged 3 times with KCl (40 mM) to test tissue viability and to obtain a consistent response. After recording the maximal response to KCl, the tissues were washed and allowed to return to baseline before the next challenge. Cumulative concentration-response curves were obtained from pleural strips by increasing the agonist concentration (sPLA<sub>2</sub>) in the tissue bath by half-log<sub>10</sub> increments while the previous concentration remained in contact with the tissues (Ref.1, supra.). Agonist concentration was increased after reaching the plateau of the contraction elicited by the preceding concentration. One concentration-response curve was obtained from each tissue. To minimize variability between tissues obtained from different animals, contractile responses were expressed as a percentage of the maximal response obtained with the final KCl challenge. When studying the

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effects of various drugs on the contractile effects of sPLA<sub>2</sub>, the compounds and their respective vehicles were added to the tissues 30 minutes prior to starting the sPLA<sub>2</sub> concentration-response curves.

5

Statistical analysis:

Data from different experiments were pooled and presented as a percentage of the maximal KCl responses (mean  $\pm$  S.E.). To estimate the drug induced rightward shifts in the concentration response curves, the curves were analyzed simultaneously using statistical nonlinear modeling methods similar to those described by Waud (1976), Equation 26, p. 163, (Ref.2). The model includes four parameters: the maximum tissue response which was assumed the same for each curve, the ED<sub>50</sub> for the control curve, the steepness of the curves, and the pA<sub>2</sub>, the concentration of antagonist that requires a two-fold increase in agonist to achieve an equivalent response. The Schild slope was determined to be 1, using statistical nonlinear modeling methods similar to those described by Waud (1976), Equation 27, p. 164 (Ref. 2). The Schild slope equal to 1 indicates the model is consistent with the assumptions of a competitive antagonist; therefore, the pA<sub>2</sub> may be interpreted as the apparent K<sub>B</sub>, the dissociation constant of the inhibitor.

To estimate the drug-induced suppression of the maximal responses, sPLA<sub>2</sub> responses (10 ug/ml) were determined in the absence and presence of drug, and percent suppression was calculated for each pair of tissues. Representative examples of inhibitory activities are presented in Table 2, below.

Ref. 1 - van, J.M.: Cumulative dose-response curves. II. Technique for the making of dose-response curves in isolated organs and the evaluation of drug parameters. Arch. Int. Pharmacodyn. Ther., 143: 299-330, 1963.

-52-

Ref. 2 - Waud, D.: Analysis of dose-response relationships. in Advances in General and Cellular Pharmacology eds Narahashi, Bianchi 1:145-178, 1976.

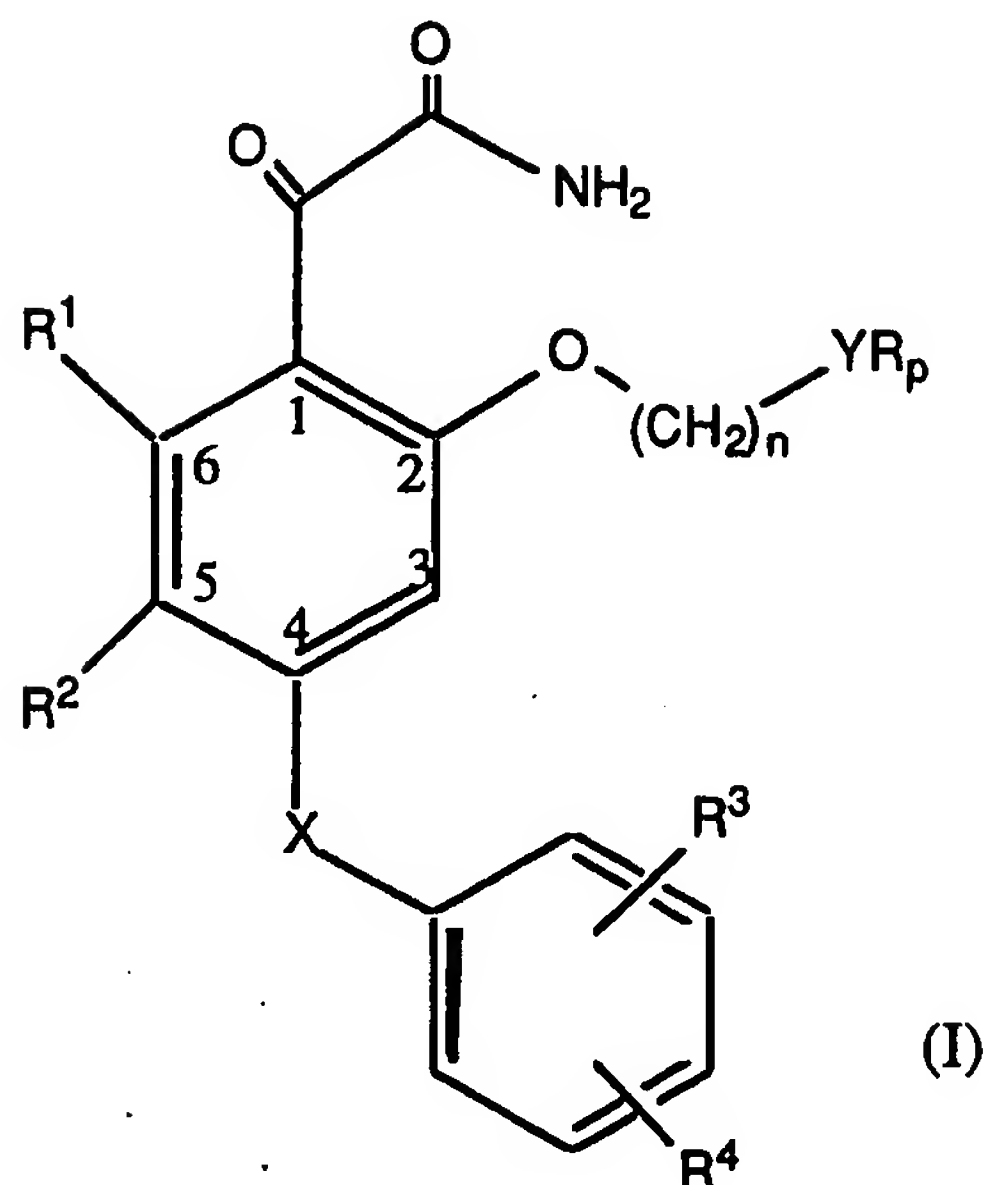
- 5 Compounds of the instant invention were tested in Assay Example 2 and were found to be effective.



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We claim:

1. A compound of the formula (I)



wherein:

X is -O- or -(CH<sub>2</sub>)<sub>m</sub>-, where m is 0 or 1;

Y is -CO<sub>2</sub>-, -PO<sub>3</sub>-, -SO<sub>3</sub>-;

10 R is independently -H or -(C<sub>1</sub>-C<sub>4</sub>)alkyl;

R<sup>1</sup> and R<sup>2</sup> are each independently -H, halo or -(C<sub>1</sub>-C<sub>4</sub>)alkyl;

15 R<sup>3</sup> and R<sup>4</sup> are each independently -H, -(C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, (C<sub>1</sub>-C<sub>4</sub>)alkylthio, halo, phenyl or phenyl substituted with halo;

n is 1-8; and

p is 1 when Y is -CO<sub>2</sub>- or -SO<sub>3</sub>- and 1 or 2 when Y is -PO<sub>3</sub>-;

or a pharmaceutically acceptable salt thereof.

20

2. A compound of formula I as claimed in Claim 1 wherein X is oxygen, Y is -CO<sub>2</sub>-, n is 4-5, R, R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are -H, and R<sup>4</sup> is phenyl or phenyl substituted with halo.

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3. A compound of formula I as claimed in Claim 1 which is 2-(4-carboxybut-1-yl-oxy)-4-(3-phenylphenoxy)phenylglyoxamide.

5 4. A pharmaceutical formulation comprising a compound of formula I as claimed in Claim 1 together with a pharmaceutically acceptable carrier or diluent therefor.

10 5. A method of inhibiting sPLA<sub>2</sub> in a mammal in need of such treatment comprising administering to said mammal a pharmaceutically effective amount of a compound of formula I.

15 6. A method of Claim 5 wherein the compound is 2-(4-carboxybut-1-yl-oxy)-4-(3-phenylphenoxy)phenylglyoxamide.

20 7. A method of selectively inhibiting sPLA<sub>2</sub> in a mammal in need of such treatment comprising administering to said mammal a pharmaceutically effective amount of a compound of formula I.

25 8. A method of Claim 7 wherein the mammal is a human.

30 9. A method of Claim 7 or 8 wherein the compound is 2-(4-carboxybut-1-yl-oxy)-4-(3-phenylphenoxy)phenylglyoxamide.

10. A method of Claim 5 of alleviating the pathological effects of septic shock, adult respiratory distress syndrome, pancreatitis, trauma-induced shock, bronchial asthma, allergic rhinitis, and rheumatoid arthritis which comprises administering to a mammal in need of such treatment a compound of formula I in an amount sufficient to inhibit sPLA<sub>2</sub> mediated release of

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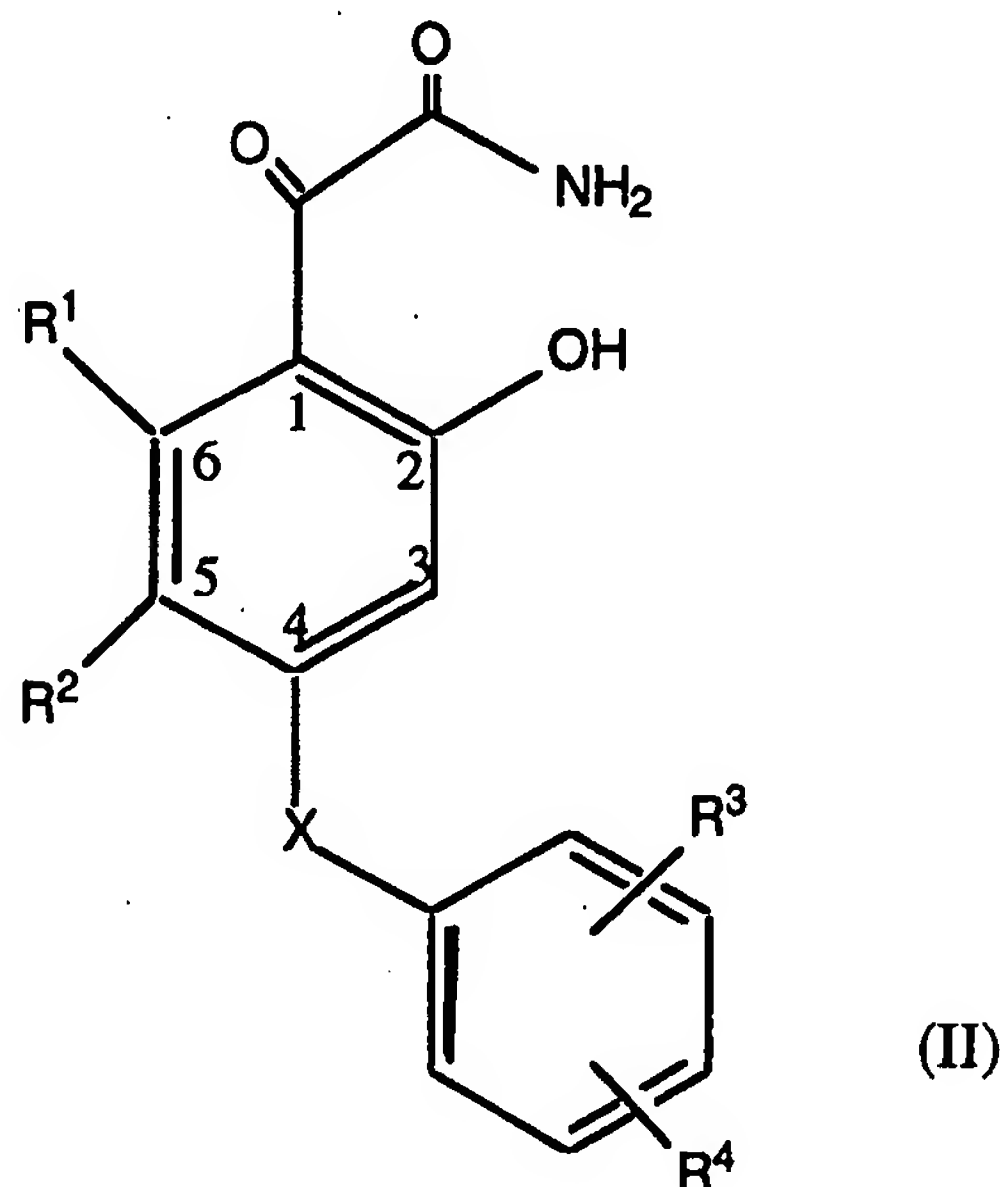
fatty acid and to thereby inhibit or prevent the arachidonic acid cascade and its deleterious products.

11. A method of Claim 10 wherein the mammal is  
5 a human.

12. A method of Claim 10 or 11 wherein the compound is 2-(4-carboxybut-1-yl-oxy)-4-(3-phenylphenoxy)phenylglyoxamide.

10

13. A compound of the formula II



15 wherein:

X is -O- or -(CH<sub>2</sub>)<sub>m</sub>-, where m is

0 or 1;

R<sup>1</sup> and R<sup>2</sup> are each independently -H, halo or -  
(C<sub>1</sub>-C<sub>4</sub>)alkyl and

20

R<sup>3</sup> and R<sup>4</sup> are each independently -H, -  
(C<sub>1</sub>-C<sub>4</sub>)alkyl, -(C<sub>1</sub>-C<sub>4</sub>)alkoxy, (C<sub>1</sub>-C<sub>4</sub>)alkylthio, halo,  
phenyl or phenyl substituted with halo.

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US97/21434

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : Please See Extra Sheet.

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 564/15, 162, 169; 560/45; 562/468, 469, 471; 514/119, 539, 563, 618, 621.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN ONLINE STRUCTURE SEARCH IN FILE REGISTRY.

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GEFFKEN, D. et al. An improved synthesis of N-alkoxy-alpha-oxo-arylacetamides. Synthetic Communications. 1996, Vol. 26, No. 22, pages 4153-4156.	1-13
A	OZAWA, F. et al. Palladium-catalyzed double carbonylation of aryl halides to give alpha-keto amides. Mechanistic studies. J. Am. Chem. Soc. 1985, Vol. 107, pages 3235-3245.	1-13
A	Chemical Abstracts., Vol. 113, No. 13, 24 September 1990 (Columbus, OH, USA), page 639, column 2, the abstract no. 114766m, BURCHARDT, A. et al. 'N-substituted 2-aryl-2-hydroxycarbohydroxamic acids.' Arch. Pharm. 1990, 323(3), 181-183 (Weinheim, Ger.).	1-13

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"B" earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means		
"P" document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

25 FEBRUARY 1998

Date of mailing of the international search report

16 MAR 1998

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## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US97/21434

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Chemical Abstracts, Vol. 122, No. 19, 08 May 1995 (Columbus, OH, USA), page 1039, column 2, the abstract no. 239485m, GEFKEN, D. et al. 'Synthesis and properties of 3-alkylsubstituted 1-alkoxy(hydroxy)indolin-2-ones.' Pharmazie. 1994, 49(12), 889-893 (Ger.).	1-13

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US97/21434

## A. CLASSIFICATION OF SUBJECT MATTER:

IPC (6):

C07F 9/02, 9/28, C07C 59/40, 59/48, 59/64, 59/84, 62/30, 63/33, 65/03, 229/00, 233/00, 235/00, 237/00, 239/00, 321/00, 323/00, 381/00; A61K 31/24, 31/66, 31/165, 31/195.

## A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

564/15, 162, 169; 560/45; 562/468, 469, 471; 514/119, 539, 563, 618, 621.